Society for Endocrinology

ISSUE 120 SUMMER 2016
ISSN 0965-1128 (PRINT)
ISSN 2045-6808 (ONLINE)

THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

Moving and shaking: THE ENDOCRINOLOGY OF MUSCLE AND BONE

Special features
PAGES 6–16

Important new guidance
ADRENAL SURGERY
P29

70 years of the Society
THE 1970s: A TURNING POINT IN PUBLISHING
P30

BONE AND CALCIUM
An Endocrine Network with big plans
P20

HORMONE-RELATED CANCER
New website launched
P21

OSTEOPOROSIS
Setting up a nurse-led clinic
P27

A word from THE EDITOR...

Sport is not always associated with the top end of the endocrine business. Be it lurid tabloid guessing games of 'Is she a *he*?', state-sponsored oral Turinabol administration in 1970s East Germany or the polypharmacy of sociopathic cyclists, hormones seem inevitably to feature for all the wrong reasons. It still baffles me when professionals who have been told 'Don't take that drug' feign shock and disbelief after detection of said drug in their bodily substance. To me, such simple instructions sit alongside other clear statements of imperative mood like 'Stop kicking when the ref blows his whistle' and 'Stand behind the white line at the start.' Read the instructions written inside the lid of the box before you play the game, or don't bother playing at all.

Still, to the average armchair idler, there is much fun to be had in watching people go faster, jump higher and be stronger than their rivals. To enhance your viewing, in this issue, we've gone for a wonderfully diverse look at bone, muscle and movement. Duncan Bassett and Colin Farquharson lay out their vision for the Society's Bone and Calcium Endocrine Network on page 20. Meanwhile, Anna Krook explores some of molecular mechanisms that underpin the benefits of exercise (page 11), while James Brousil and Andrew Robinson's article serves as an excellent reminder that bone is far more interesting than a collection of inert scaffolding tubes (page 9).

While few will ever come close to Olympic fitness, many of us will be living longer, with a need to maintain our bone health for as long as possible. On page 6, Rosemary Bland highlights some of the (still!) ongoing controversy around vitamin D while, on page 8, Richard Eastell sets out the current anti-osteoporosis armamentarium. In addition, Louise Foley and colleagues highlight their work in bringing academic rigour into the hugely important world of the built environment (page 15).

Finally, Saffron Whitehead (page 17) and Bernard Donovan (page 30) have supplied two very personal accounts of their early careers, reminding me again that the past really is a foreign country, where they do things differently.

Have a great summer.

TONY COLL

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Registered in England No. 349408
Registered Office as above
Registered Charity No. 266813

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CONTENTS

You can view this issue online:
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ON THE COVER...
P6–16
ENDOCRINOLOGY OF BONE AND MUSCLE
The latest research

NEW GUIDANCE
P29
ADRENAL SURGERY
Time for change

Become a contributor... Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the Autumn 2016 issue: **11 July 2016**.
Deadline for news items for the Winter 2016 issue: **26 September 2016**.

Front cover image ©SHUTTERSTOCK

NEW EDITOR-IN-CHIEF

The Society for Endocrinology's open-access journal *Endocrine Connections* has a new Editor-in-Chief: Professor Josef Köhrle. Professor Köhrle is the Scientific Director of the Charité Centre for Therapeutic Research at Universitätsmedizin Berlin, Germany. His research focuses on the biosynthesis, transport, uptake, binding, metabolism and action of thyroid hormones and their metabolites.

JOIN A SOCIETY COMMITTEE!

DEADLINE 30 JUNE

There are vacancies on Council, the Clinical, Nurse, Programme, Public Engagement and Science Committees, Early Career Steering Group and the Corporate Liaison Board from January 2017. If you would like to stand for election to one of these groups, please complete a nomination form, which can be found on the specific Committee web pages at **www.endocrinology.org/about/committee.html**. Self nominations are accepted.

CONGRATULATIONS!

Many congratulations to Liz Glenister (third from left) from Hypopara UK, who has been chosen as Britain's Best Volunteer 2016 in recognition of her work for the charity. After her own experience, Liz founded Hypopara UK 11 years ago, as a place where people with parathyroid conditions could find information and support. On winning the prestigious award, Liz said, 'I'm absolutely thrilled to have won, which I see as a fantastic opportunity to raise awareness about this rare condition and our small, but far-reaching, charity.' Well done Liz!

UNDERGRADUATE ACHIEVEMENT AWARD 2016

Do you know an outstanding undergraduate who deserves recognition? Apply now for the Society's Undergraduate Achievement Award, which recognises and promotes excellence in the study of endocrinology. It comprises a grant of £300 per year for 3 years to your department and, upon request, certificates from the Society to the award-winning students.

This flexible award may, for instance, recognise a specific endocrine-related piece of work, such as a project or essay, or may be awarded to the top-scoring student for an exam piece.

Applications open on 15 June and close on 13 July 2016.

Find out more at **www.endocrinology.org/grants**.

STUDENT ESSAY PRIZE

Many congratulations to Alastair Macfarlane from King's College London for winning first prize in the 2016 Student Essay Prize for 'Homer Simpson: can personalised medicine save TV's most famous anti-hero? The cartoon glutton and his obesity'.

NEW SOCIETY VIDEO

The Society's new video tells you more about what we do, who our members are, and our aims in supporting you – our community – in the advancement of endocrinology. You can watch it on the Society's YouTube channel.

FREE STUDENT PLACES AT SFE BES 2016!

Do you know a student or undifferentiated trainee who would benefit from a free place at SfE BES 2016? Nominate them today for a Society for Endocrinology BES Registration Grant.

Applications close on 4 July 2016. Find out more at **www.endocrinology.org/grants**.

WITH REGRET

We're sorry to report the sad news of the death of Dennis Wang.

He died peacefully on 3 March 2016 after suffering long-term with Parkinson's disease. He will be remembered for his important contributions to breast cancer epidemiology (famously called The Guernsey Study) and for his amazing wit and sense of humour.

He is survived by two daughters, Liz and Rosie.

SOCIETY CALENDAR

7–9 November 2016
SfE BES CONFERENCE 2016
Brighton

www.endocrinology.org/meetings for full details

SOCIETY SUPPORTED EVENTS

14 July 2016
REGIONAL CLINICAL CASES MEETING
Norwich

15–16 September 2016
HORMONE DEPENDENT CANCERS: NEW THERAPIES AND MECHANISMS OF RESISTANCE
Cambridge

18–21 September 2016
12TH INTERNATIONAL WORKSHOP ON RESISTANCE TO THYROID HORMONE
Colorado Springs, CO, USA

GRANT AND PRIZE DEADLINES

15 JUNE 2016
ENDOCRINE NURSE AWARD

15 JUNE 2016
REGIONAL CLINICAL CASES MEETING GRANTS

3 MAY–4 JULY 2016
SfE BES REGISTRATION GRANTS

15 JUNE–13 JULY 2016
UNDERGRADUATE ACHIEVEMENT AWARDS

15 AUGUST 2016
TRAVEL GRANTS

27 NOVEMBER 2016
EARLY CAREER GRANTS

27 NOVEMBER 2016
EQUIPMENT GRANTS

www.endocrinology.org/grants for full details of all Society grants

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology, Journal of Molecular Endocrinology, Endocrine-Related Cancer* and *Clinical Endocrinology* via the members' area on the Society home page, **www.endocrinology.org**. *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access (OA) and free to all.

JOURNAL OF ENDOCRINOLOGY

The circadian clock in pregnancy-induced adaptations

The hypothalamic-pituitary-adrenal axis plays a central role in maternal physiological adaptations to pregnancy. Wharfe *et al.* set out to determine if these changes are mediated via the clock rhythm genes in the hypothalamus.

Using a mouse model, they found that expression of all the clock genes in the anterior hypothalamus varied markedly throughout gestation. Maternal corticosterone levels increased significantly (up to 14-fold on day 14 of pregnancy), but this was not accompanied by a similar alteration in plasma adrenocorticotrophin (ACTH) levels, which were 28% lower on day 14 compared with non-pregnant levels. Additionally, the daily circadian release of corticosterone was maintained up to day 14 of gestation, but this rhythm was lost by day 18.

Overall, the data indicate that while changes to the central circadian clock during pregnancy are likely to contribute to maternal physiological adaptations, neither these hypothalamic clock genes nor plasma ACTH levels seem to power the increase in maternal corticosterone after mid-gestation.

Read the full article in *Journal of Endocrinology* **228** 135–147

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Maternal high-fat diet and stroke outcome in offspring

Parental heredity, environmental factors and adult lifestyle are well known to contribute to the development of health issues. Lin *et al.* have explored the effects of maternal high-fat diets (HFDs) on stroke outcomes in adult offspring.

Four experimental parameters were tested in Sprague–Dawley rats: the effects on offspring from dams fed with either normal chow or HFDs during gestation and lactation, with resulting male pups fed with either normal chow or HFDs for 120 days. Ischaemic stroke was surgically induced via middle cerebral artery occlusion and parameters including body weight, glucose tolerance, infarct volume, neuronal sensitivity, brain-derived neurotrophic factor (BDNF) expression and hypothalamic-pituitary-adrenal (HPA) axis were assessed.

The researchers found increased infarct volume, decreased BDNF expression and alteration in the sensitivity of the HPA axis in offspring from dams fed with the HFD, showing how an HFD may alter key circuitry, reprogramming post-stroke events with alterations of post-stroke outcomes.

Read the full article in *Journal of Molecular Endocrinology* **56** 101–112

ENDOCRINE-RELATED CANCER

GHRH excess and blockade in X-LAG syndrome

X-linked acrogigantism (X-LAG) syndrome is a recently described, inheritable form of pituitary gigantism, resulting from micro-duplication on chromosome Xq26.3, including *GPR101*. The aetiology of X-LAG includes onset in early childhood and markedly high growth hormone (GH) and prolactin secreted from mixed pituitary hyperplasia/adenomas. The nature of X-LAG syndrome makes it challenging to control growth, even when employing multiple treatment modalities.

Daly *et al.* aimed to decipher the mechanism(s) driving hyperplasia, adenoma formation and secretory behaviour *in vitro*, using primary pituitary cell culture of an adenoma obtained from a female patient with X-LAG syndrome. GH-releasing hormone (GHRH), GH and prolactin were detected in primary pituitary adenoma cell-conditioned media. The GPR101 agonist GHRH1–5 had marginal effects on GH secretion, but no effect on prolactin release. Treatment with a GHRH receptor antagonist inhibited both GH and prolactin secretion, reversible by incubation with GHRH.

This study suggests that the GHRH pathway may be an important therapeutic target for controlling the hormonal secretion observed in X-LAG syndrome.

Read the full article in *Endocrine-Related Cancer* **23** 161–170

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

High five: evolution of frog 'foot flag' display

To attract a mate, many frog species use multimodal displays, which may include croaking and body and leg movements. Little is known of how selection pressure for these displays may drive evolution of other systems within the body, including androgenic sensitivity.

Mangiamele *et al.* studied the 'foot flag' display of the male Bornean rock frog (*Staurois parvus*; pictured). Administration of testosterone led to a significant increase in 'foot flagging' behaviour. Quantitative PCR showed that the frogs' hind limb muscles (which produce the display) have significantly higher androgen sensitivity when compared with other closely related species, mediated by an approximately tenfold higher expression of androgen receptor in these muscles in *S. parvus*.

This implies that 'foot flagging' is an androgen-dependent signal, and its recent evolution in this frog species is associated with increased androgen sensitivity in the muscles used to produce it.

Read the full article in *Proceedings of the National Academy of Sciences of the USA* **113** 5664–5669


©Doris Preninger

Hot Topics is written by Rosemary Bland, Dominic Cavlan, Tony Coll, Jennie Evans, Kim Jonas and Amir Sam.

CLINICAL ENDOCRINOLOGY

Long term pegvisomant for acromegaly

The growth hormone receptor antagonist pegvisomant may be used in patients with acromegaly who are not cured by transsphenoidal surgery and resistant to somatostatin analogues.

Ramos-Leví *et al.* evaluated the outcomes of long term pegvisomant therapy for acromegaly in 64 patients from tertiary care referral hospitals in Spain. Patients were followed-up for 9 (4.1–10.4) years after the first administration of pegvisomant in a clinical setting. Insulin-like growth factor-1 normalisation was achieved in almost 90% of patients. Tumour growth was seen in about 9% of patients, none of whom had received prior radiotherapy.

Loss of biochemical control ('escape') occurred in approximately 16% of patients, but could be relatively easily overcome by adjusting therapy. Potential underlying causes of escape included tumour regrowth, lipohypertrophy, previous treatment modifications, concomitant menopause, change in testosterone administration and acute concomitant administration of high glucocorticoid doses.

The authors give reassurance regarding the efficacy and safety of long term pegvisomant, and highlight the importance of close follow-up and adequate pegvisomant dose titration.

Read the full article in *Clinical Endocrinology* **84** 540–550

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Fluconazole in treatment of Cushing's disease

The limited availability of ketoconazole for use in suppressing steroidogenesis in Cushing's disease has been problematic in recent years. This was a problem faced by Burns *et al.* when treating a patient with a 4mm corticotroph pituitary adenoma whose symptoms recurred 6 months after transsphenoidal surgery.

Medical control was not achieved with metyrapone alone, so ketoconazole (400mg daily) was added with good effect, but became unavailable. Fluconazole is an alternative azole compound used to treat fungal infections, with fewer side effects (particularly hepatotoxicity) than ketoconazole.

The introduction of fluconazole at 200mg daily, and a subsequent increase to 400mg daily, saw medical control achieved. Following external beam radiotherapy, treatment with fluconazole alone was sufficient to achieve biochemical control. The authors propose that it be considered for use in the medical management of Cushing's disease.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* **2** 2016 EDM-15-0115

ENDOCRINE CONNECTIONS

Renin-angiotensin system in endometrial cancer

Endometrial cancer is the most common gynaecological malignancy. Risk factors include obesity, hypertension, diabetes and hyperoestrogenism – all of which are linked to activation of the renin-angiotensin system (RAS). The endometrium expresses all of the components of the RAS in both glandular and stromal cells, with levels varying though the menstrual cycle.

The endometrial RAS has been implicated in angiogenesis, neovascularisation and cell proliferation, factors which are involved in tumour growth and spread. Overexpression of angiotensin II and its receptor have been found in several malignancies, while a reduction in the relative risk of cancer has been demonstrated in patients using angiotensin-converting enzyme (ACE) inhibitors for hypertension.

Over-activation of the RAS can be attributed to single nucleotide polymorphisms (SNPs) in RAS genes. Pringle *et al.* measured the prevalence of five polymorphisms in RAS genes in 184 Australian women with endometrial cancer and in healthy controls. They found SNPs in the genes for angiotensin II and the angiotensin II receptor which are predicted to increase RAS activity, and which were associated with a statistically significant increase in the prevalence of endometrial cancer.

Read the full article in *Endocrine Connections* doi: 10.1530/EC-15-0112 (OA)

Cardiovascular effects of maternal stress

Environmental challenges, such as maternal stress, can significantly affect fetal growth and health outcomes throughout life. While the full role of the placenta in mediating these effects is uncertain, studies have shown that the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which catalyses the conversion of cortisone to cortisol, must play a key role.

Using mice lacking 11β-HSD2 to model maternal stress, Wyrwoll *et al.* explored its consequences for fetal cardiovascular development, and whether the effects are reversible. They found evidence that cardiovascular development was impaired in *Hsd11b2*$^{-/-}$ fetuses; these didn't experience the normal gestational increase in umbilical vein blood velocity or the decline in resistance index in the umbilical artery exhibited by their *Hsd11b2*$^{+/+}$ littermates. Evidence of fetal growth restriction and retarded heart development was also found. However, treatment with pravastatin improved all these parameters in *Hsd11b2*$^{-/-}$ fetuses.

This suggests that statins may be useful therapeutically in addressing intrauterine growth retardation due to placental vascular hypofunction, but it remains to be seen whether these effects translate to humans.

Read the full article in *Proceedings of the National Academy of Sciences of the USA* doi:10.1073/pnas.1520356113

Maybe the dog really DID eat your homework...

In developed countries, almost 60% of dogs are overweight. The increased level of obesity mirrors that in humans, implicating factors such as reduced exercise and ready access to high calorie food. However, some dog breeds are particularly obesity-prone, suggesting the influence of genetic factors.

In a study of 310 pet and assistance dog Labradors, Raffan *et al.* found that a 14bp deletion in the pro-opiomelanocortin (POMC) gene, which results in the disruption of β-melanocyte-stimulating hormone and β-endorphin, was associated with increased body weight, adiposity and food motivation in both Labrador Retrievers and closely related Flat-Coated Retrievers. In both breeds, for each copy of the deletion carried, the dog was on average 1.9kg heavier.

The mutation was significantly more common in Labrador Retrievers selected to become assistance dogs than was the case in pets. As 'trainability' is important in the selection of assistance dogs, and 'positive reinforcement' with a food reward is a mainstay of puppy training, it may be that dogs carrying the POMC deletion are more likely to be selected as assistance dogs.

Read the full article in *Cell Metabolism* doi:10.1016/j.cmet.2016.04.012

Long term effect of gestational diabetes

Gestational diabetes mellitus (GDM) affects approximately 1 in 20 pregnancies in the UK, and can have adverse health implications for mother and infant.

Logan *et al.* conducted a prospective longitudinal study in 86 infants using magnetic resonance imaging scans to assess how body fat in offspring of mothers with GDM differed from those without GDM over the first 3 months following birth. GDM had been well-controlled in all cases, and breastfeeding rates were similar in the two groups during the course of the study (GDM group, 71%; control group, 74%). Despite there being no difference in body fat content at birth, at 10 weeks of age, infants born to mothers with GDM had significantly more body fat than those born to unaffected mothers.

The reasons for this are unclear, but the finding suggests that adiposity in infants whose mothers had GDM is amplified early in infancy, indicating a potential causal pathway to later adverse metabolic health.

Read the full article in *Diabetes Care* doi:10.2337/dc16-0030

VITAMIN D DEFICIENCY: IS IT REALLY A PROBLEM – AND WHAT'S THE SOLUTION?

WRITTEN BY ROSEMARY BLAND

Vitamin D deficiency is considered a global problem. Limited exposure to sunlight, due to location or lifestyle choices, is often cited as the cause of this epidemic. However, is deficiency that prevalent and, if so, what can be done about it?

WHY DO WE NEED VITAMIN D?

Vitamin D deficiency is associated with disorders of bone and mineral metabolism and, in particular, the development of rickets and osteomalacia. However, there is growing evidence that vitamin D has a crucial role in the immune system: facilitating the normal response to infection and regulating inflammatory responses and autoimmune disease. It also maintains muscle strength, may prevent falls, and could lower the risk of developing cancer, cardiovascular disease and diabetes.

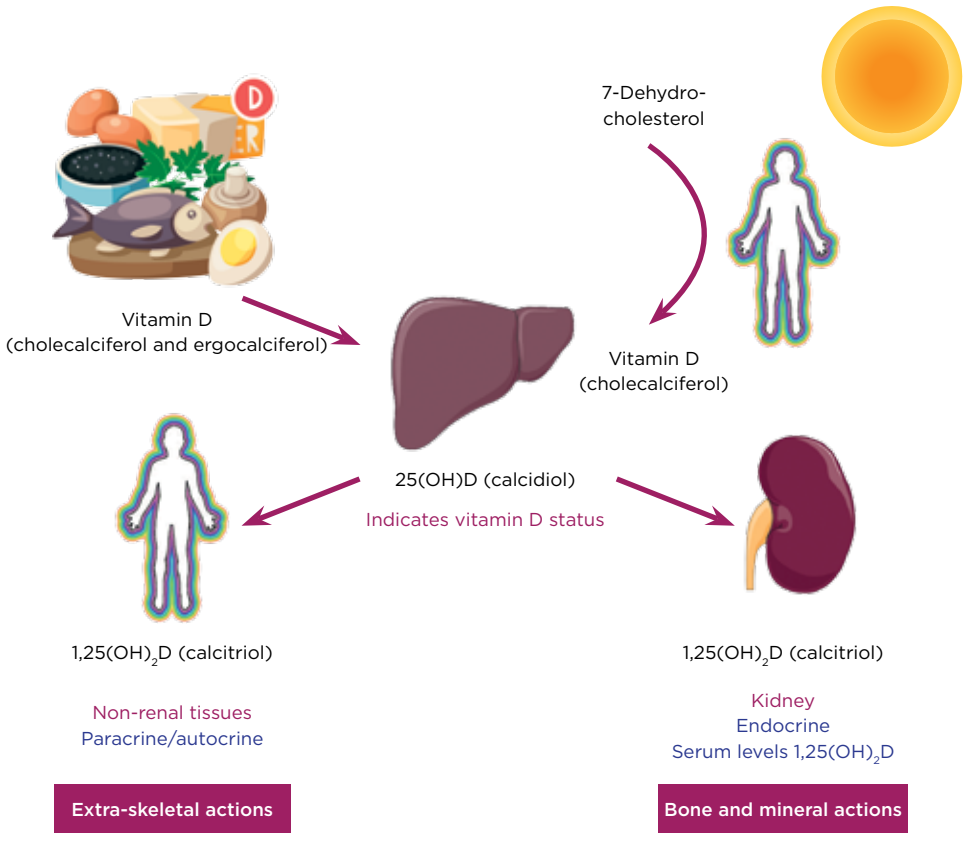
HOW DO WE OBTAIN IT?

Vitamin D is found in foods such as oily fish, dairy products and mushrooms. However, for most people, the dietary intake of vitamin D is relatively low and the majority of it is synthesised (Figure). The key step is the conversion of 7-dehydrocholesterol in the skin to vitamin D (cholecalciferol), a reaction mediated by ultraviolet light (wavelength 290–320nm). Production of 25-hydroxyvitamin D (25(OH)D; calcidiol) by the liver is dependent on vitamin D availability. As such, serum 25(OH)D is considered a good indicator of vitamin D status.

HOW MUCH DO WE NEED?

There isn't a consensus on what constitutes a healthy vitamin D level. Vitamin D isn't considered in terms of a normal range. Instead, people are classified as having deficient, insufficient or adequate levels of serum 25(OH)D. But where should those boundaries lie? Are the serum 25(OH)D thresholds required to maintain skeletal health the same as those required for extra-skeletal outcomes, and do thresholds vary with population subgroups?

The National Osteoporosis Society suggests that a level <30nmol/l is deficient, 30–50nmol/l is insufficient and >50nmol/l is adequate.[1] The Scientific Advisory Committee on Nutrition (SACN) is currently reviewing guidance for vitamin D. The draft report was published in 2015 with the final report due later this year. They concluded that, to ensure the musculoskeletal health of the population (97.5% of individuals) is protected, serum 25(OH)D levels should not fall below 25nmol/l at any time of the year.[2]



Vitamin D is obtained from the diet or synthesised in the skin by the conversion of 7-dehydrocholesterol, a reaction mediated by UV light (290–320nm). Hydroxylation of vitamin D in the liver produces 25-hydroxyvitamin D (25(OH)D; calcidiol). A further hydroxylation step, catalysed by 25(OH)D 1α-hydroxylase, produces the active hormone 1,25-dihydroxyvitamin D (1,25(OH)$_2$D; calcitriol). Liver/kidneys ©Servier Medical Art; Person ©Clipart.co; Vitamin D ©Shutterstock

Although most people in the field were disappointed that they had set the level so low (the Institute of Medicine concluded that serum 25(OH)D levels should be 50nmol/l), we should remember that this is an absolute minimum for everyone.

HOW WIDESPREAD IS THE DEFICIENCY?

Data from the National Diet and Nutrition Survey indicated that, across the year, 21.8% of all UK adults were deficient (<25nmol/l) and 61.4% had insufficient levels (<50nmol/l). These percentages increased significantly in certain populations, with 53–80% of adult Asian women having serum 25(OH)D below 25nmol/l. This is reflected across Europe, although notable exceptions were found, such as in Greece![3] Deficiency in young children is significant, and is manifested by an increase in rickets.

HOW CAN WE MAINTAIN ADEQUATE LEVELS?

Sunlight exposure correlates with 25(OH)D levels. Until very recently, it had been thought that advocating safe sun exposure (10–15 minutes per day in the summer) coupled with a healthy diet would ensure adequate vitamin D levels (currently supplements are only recommended for individuals at risk of deficiency). However, this is unlikely to be the case.

This is where the SACN recommendations make interesting, although possibly controversial, reading. SACN calculated that, to achieve a serum 25(OH)D ≥25nmol/l in winter, it is necessary to have a vitamin D intake of approximately 10µg (400IU) per day. It is unlikely that this could be achieved by a change in diet. This leaves two options: food fortification or supplementation.

Both options are controversial. Is it reasonable, or possible, to consider supplementing the whole population? Licensed vitamin D products have only been available in the UK for the last few years, and could everyone have a prescription for vitamin D? Over the counter vitamin D supplements are classified as health foods and are therefore not subject to the same controls as pharmaceutical products. The actual concentration of vitamin D per dose versus what is claimed by the products has been found to range from 14% to 150%, and they may contain potential allergens.

So what about food fortification? A few food items are voluntarily supplemented with vitamin D, and this is used positively in marketing material. However, the UK is generally reticent to accept mandatory food fortification, fluoride in water being the exception. Interestingly, there is an example of a widespread hormonal deficiency that was corrected by food fortification – that of iodine supplementation of salt to correct a worldwide thyroid hormone deficiency.

Awareness of vitamin D deficiency is growing; however there is a reluctance to accept the potential scale of the problem. It will be interesting to see the response to the SACN guidelines and how vitamin D deficiency is addressed in the next few years.

ROSEMARY BLAND
University of Warwick and University Hospitals Coventry and Warwickshire NHS Trust

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OSTEOPOROSIS: ADVANCES IN TREATMENT

WRITTEN BY RICHARD EASTELL

We have seen quite striking changes in the management of osteoporosis over the last two decades. 25 years ago, the only effective treatment in use was hormone replacement therapy (HRT).

We no longer use HRT for postmenopausal osteoporosis, because the risks outweigh the benefits. Fortunately, since the advent of the bisphosphonate etidronate, several other treatments have also been licensed for use in osteoporosis (see Table). We are guided in the use of these agents by NICE guidance (CG146, TA160, TA161, TA204).

PROS AND CONS OF BISPHOSPHONATES

In practice, we often start with an oral bisphosphonate. The most commonly used is alendronate, given at a dose of 70mg once a week. This treatment has proved to be effective and safe at reducing the risk of fractures in patients with osteoporosis.

We have become aware that such treatment can be associated with long term adverse effects, such as atypical femur fractures and, more rarely, osteonecrosis of the jaw. As a result, the use of drugs such as alendronate has changed, and we often recommend a 'drug holiday' after their use for 5 years, unless the bone mineral density (BMD) is still in the osteoporosis range or there have been low trauma fractures (such as vertebral fractures) whilst on treatment. If we continue, we still stop after 10 years of treatment.

ALTERNATIVE APPROACHES

Not all patients can tolerate oral bisphosphonates as they can irritate the oesophagus. It is fortunate that we have drugs that can be given parenterally that are at least as effective, namely zoledronic acid (given as a 5mg annual infusion) or denosumab (a RANKL inhibitor given 6-monthly as a subcutaneous injection).

Treatments licensed for use in postmenopausal osteoporosis

Anti-catabolic	
Bisphosphonates:	Etidronate, 1991
	Alendronate, 1995
	Risedronate, 1998
	Ibandronate, 2003
	Zoledronic acid, 2008
Strontium ranelate, 2004	
Denosumab, 2010	
Anabolic	
Teriparatide, 2003	
Intact parathyroid hormone, 2006	

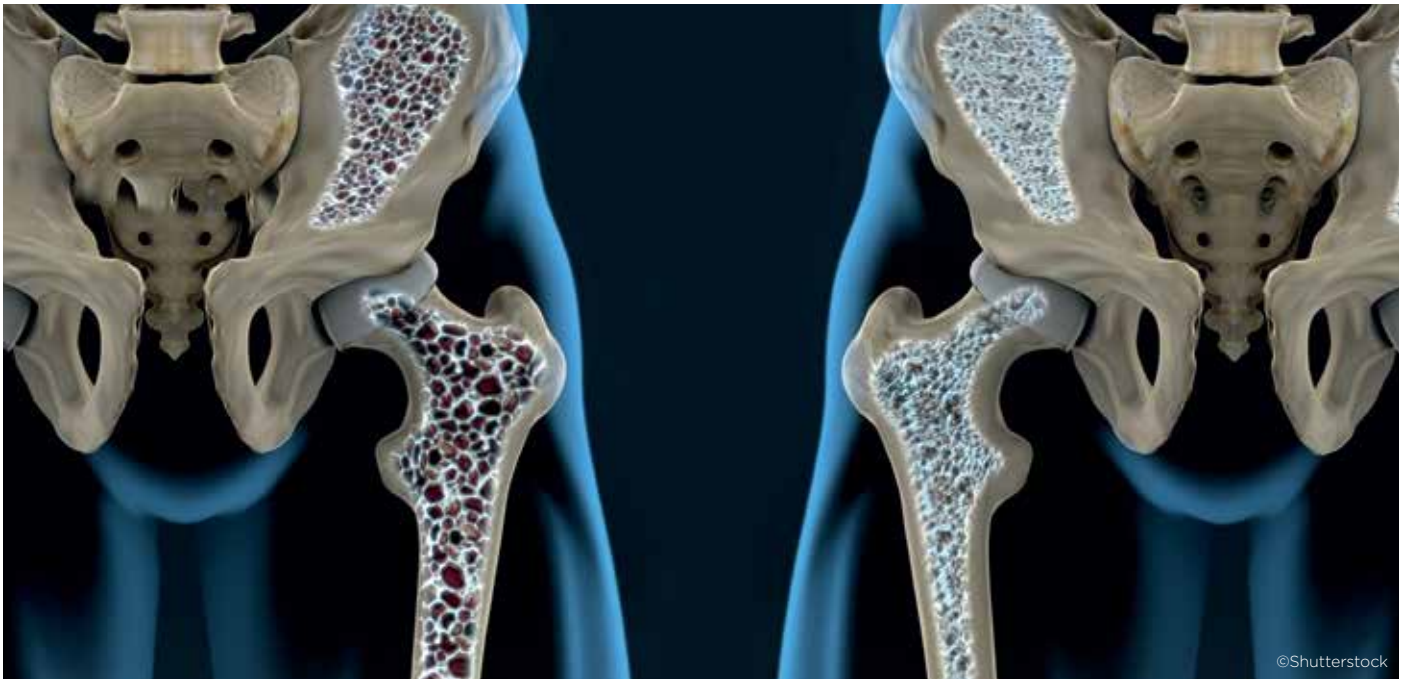
We can also use anabolic treatment (now only teriparatide as intact parathyroid hormone (PTH) is no longer available) in severe osteoporosis (that is, in patients with very low bone density with vertebral fractures who are unable to tolerate oral bisphosphonates). Teriparatide is a particularly useful treatment in glucocorticoid-induced osteoporosis, but the treatment duration is limited to 2 years and its use involves a daily subcutaneous injection.

There have been recent publications in which teriparatide and denosumab have been given together and the effects on BMD have been particularly large.

NEW DRUG DEVELOPMENT

Advances in our understanding of bone biology have allowed the development of new drugs, particularly ones that are anabolic.

Several treatments with new mechanisms of action may be licensed soon. These include an anti-sclerostin antibody, romosozumab, that stimulates bone formation for up to 6 months. The highest dose increases spine and hip BMD by about 11% and 4% respectively over just 12 months of administration.[1] Preliminary reports from FRAME (the FRActure



©Shutterstock

study in postmenopausal woMen with ostEoporosis) indicate that 1 year of treatment reduces the risk of vertebral fracture by 75%, but with no significant reduction in risk of non-vertebral fractures.[2] Complete results from ongoing trials will determine whether short term treatment with an anti-sclerostin antibody offers greater anti-fracture efficacy than denosumab or zoledronic acid.

Abaloparatide, an analogue of PTH-related peptide, binds to the PTH 1 receptor, like teriparatide. It has been used for 18 months in the doses intended for use in practice, and it increases BMD of the spine and hip to a somewhat greater degree than teriparatide.[3] In the ACTIVE trial (Abaloparatide Comparator Trial in Vertebral Endpoints), there was an 86% reduction in risk of vertebral fractures and 43% decrease in risk of non-vertebral fractures.[4] Full details about its safety have not been published, but, if approved for use, abaloparatide may be a new option for treatment of patients at high risk of fracture. It has the advantage of not requiring storage in a refrigerator.

Odanacatib inhibits cathepsin K and hence the resorption of collagen matrix, but permits formation of bone and, perhaps, a more favourable bone balance, with a modest decrease in resorption and reduced inhibition of formation.[5] LOFT (the Long-Term Odanacatib Fracture Trial) found a 47% decrease in risk of hip fracture and 54% decrease in risk of vertebral fractures, along with rare instances of atypical femoral fractures and occasional morphea-like skin lesions.[6] The full safety profile of odanacatib is still being analysed.

Thus a number of treatments are on the horizon, and could further benefit our patients with osteoporosis.

RICHARD EASTELL
Academic Unit of Bone Metabolism, Metabolic Bone Centre, Northern General Hospital, Sheffield

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AN ORTHOPAEDIC VIEW OF BONE

WRITTEN BY JAMES BROUSIL & ANDREW H N ROBINSON

The skeleton hanging in the corner of the medical school lecture theatre is an image familiar to us all: an image of medical learning, but also of death. By inference, we see bone as lifeless support, iron girders, for the living soft tissues. However, we are beginning to understand the cellular and molecular functions of bone. It has unique adaptive and regenerative abilities, which allow it to heal and strengthen itself in response to the physiological demands placed upon it. Is musculoskeletal science about to move – away from biomaterials and 'replace and fix' – to a biological future of stem cells and chemical manipulation?

A LIVING STRUCTURE

The functional unit of bone is the osteon. Contained within these linear structures are the mineral and biological matrices required to maintain bone integrity. These units communicate via lacunae to allow a co-ordinated response to local environmental factors, which influence bony growth. They are separated by boundaries called cement lines (Figure 1). Fractures propagate along cement lines under torsional or bending stress. This structure also gives cortical bone its resistance to deformity when compressed.

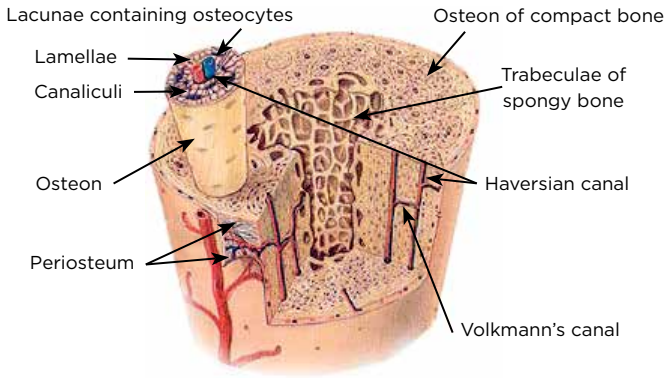

Figure 1. Section through compact bone and spongy (cancellous) bone showing the osteon – the functional unit of bone. ©U.S. National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program

Imagine then a structure which is brittle, which fatigues and fractures with repetitive eccentric load, as in the human gait cycle. Are we condemned to a life of repetitive stress fractures? Evidently not, and our saviour in all this is electricity.

Bone generates an electrical field – a piezoelectric charge – when stressed in compression. The piezoelectric charge is not from the mineral content in bone, but arises from the dipole charges in collagen as it undergoes shear

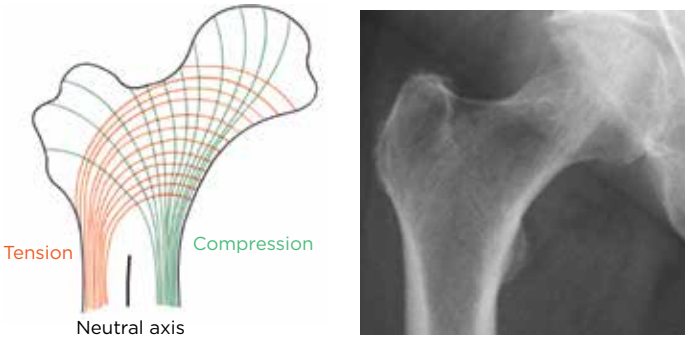

Figure 2. The piezoelectric effect demonstrated in the hip. Diagram: OpenStax College; X-ray ©Somford MP et al. 2009 *International Journal of Rheumatology* doi:10.1155/2009/253432

stress in response to load. The osteoblasts align along regions of negative charge, along the compressive lines of force (Figure 2). The osteoblasts lay down bone. The opposite is true for areas exposed to tension, or positively charged, where osteoclastic activity is increased. In this way bone adapts structurally to load.

AN AGEING SOCIETY

Bone is dynamic and continually remodelling, but we live in an ageing society. In our ageing society, osteoporosis is an epidemic. Bisphosphonates are widely prescribed and highly effective at limiting bone loss in these patients.

Their overall profile is one of bone protection, although there is an up to 47 times higher rate of insufficiency fracture of the femur.[1] Radiologically, the bone forms a 'beak', which progresses to a radiolucent stress fracture (Figure 3). These fractures are the result of bisphosphonates uncoupling bone turnover and preventing bone remodelling. The term 'frozen bone' is often used to describe the local environment of such a fracture, and healing of these fractures is often slowed. Thus, after surgery to stabilise the fracture, the race between fracture healing and implant failure (as all implants will break given time) is tilted towards implant failure. Reversal of this side effect of bisphosphonates remains an unsolved problem.

STIMULATION OF BONE HEALING

Non-union also occurs in bone with normal turnover. In response to this problem, adjuncts to stimulate bone healing have become a focus of research. Available compounds can be regarded as osteoinductive or osteoconductive.

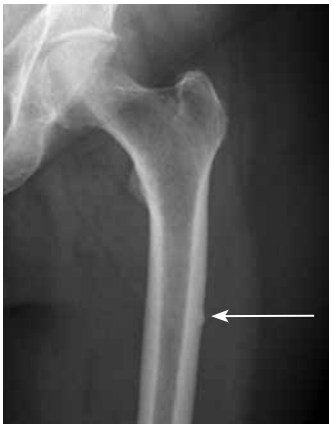

Figure 3. A 'bisphosphonate fracture' in the subtrochanteric region of the hip. The characteristic 'beaking' is demonstrated (arrow). ©Somford MP *et al.* 2009 I*nternational Journal of Rheumatology* doi:10.1155/2009/253432

The conductive substances are scaffolds which rely on local biology to populate the structures with cells. Examples include bioglass, corals, bone pastes and bone allografts. All of these substances are replaced over time by creeping substitution of bone into the graft site.

Osteoinductive substances drive the formation of new bone. Bone morphogenic proteins (BMPs) are a group of inductive adjuncts in common use. BMPs occur naturally and are part of the transforming growth factor β family. These factors are secreted by local bone matrix cells and induce cell division, matrix synthesis and tissue differentiation to promote bone formation. The use of BMPs remains in its infancy in routine fracture management but, in the future, as production costs decline and efficacy improves, these substances could drastically reduce fracture healing times and make non-union of high energy injuries a thing of the past.[2]

LOOKING TO THE FUTURE

In treating the degenerative skeleton, total hip replacement is extraordinarily effective, and is probably the most successful lifestyle operation ever devised. Nevertheless, the technology surrounding arthroplasty is now mature and unlikely to evolve dramatically in the future.

Have we reached the end of the story? Probably not. There are two likely avenues of progress: first, joint protection and, secondly, regenerative techniques.

Following intra-articular trauma, we know that secondary degeneration is not simply the product of physical damage, but is mediated separately by chemical factors. For example, we know that interleukin 1 (IL-1) levels remain raised in the synovial fluid after injury. Interestingly, IL-1 inhibitors have been used in murine models to prevent the onset of arthritis after trauma.[3]

This technology translated into the clinical setting could eventually see attempts to minimise post-traumatic degeneration after healing. Corroborative data from human synovial fluid already exist, so the practical application of this technology is not just fantasy.

On the regenerative front, we are already seeing chondrocyte implantation being used to resurface joints, although in the future it may be that we can make use of biological scaffolds, implanted with chondrocytes, to resurface and reconstitute the joint.[4]

Thus, molecular biology, at both the chemical and cellular levels, is likely to have an increasing role in the future of orthopaedics. Perhaps musculoskeletal biology, rather than bioengineering, of cells, rather than iron girders, is the future of orthopaedic intervention?

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MOVING MUSCLE MOLECULES: THE BENEFICIAL EFFECTS OF EXERCISE IN SKELETAL MUSCLE

WRITTEN BY ANNA KROOK

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Increased time spent exercising is positively linked to a reduction in all-cause mortality.[1,2] Furthermore, lack of physical activity is a significant risk factor for development of many prevalent non-communicable diseases, ranging from various forms of cancer, type 2 diabetes, cardiovascular disease and hypertension to Alzheimer's disease and depression.

Physical activity is linked to increased number of healthy years. It has been proposed that when it comes to reducing the risk of virtually all chronic diseases simultaneously, there is probably no single intervention with a higher therapeutic potential than physical exercise, and this with few or no adverse side effects.[3]

Exercise results in a plethora of changes in several different organs, including effects on the cardiovascular system, muscle and bone. This review focuses on exercise-mediated effects in skeletal muscle.

MUSCULAR ADAPTATION

Skeletal muscle is a highly plastic and adaptive organ. Muscle contraction is a physiological stress to the muscle, which responds by remodelling gene expression to adapt to increased functional demands. The well-trained muscle is characterised by changes in contractile proteins and function, and enhanced mitochondrial function and content.[4]

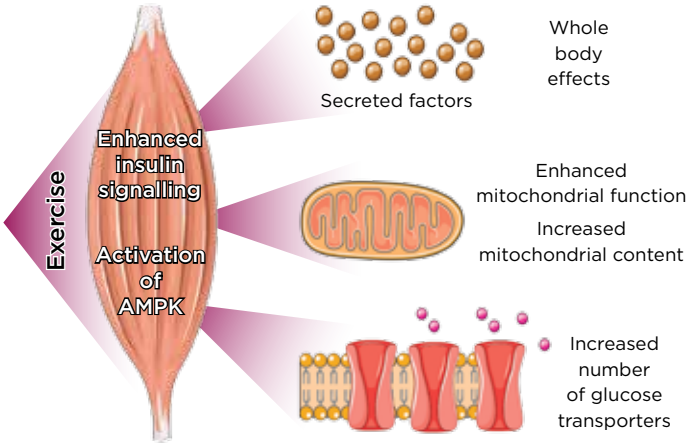
The trained skeletal muscle is stronger, has higher endurance, and is able to more efficiently utilise and switch between different nutrient sources. While exercise-induced muscle growth is perhaps a more intuitively appreciated response to muscle use, it is the exercise-mediated changes in the capacity for substrate metabolism and insulin sensitivity that probably have the more important implications for overall health.

PHYSICAL ACTIVITY AND DIABETES

The positive effects of physical activity are well documented for type 2 diabetes.[5] Skeletal muscle is an insulin-responsive organ and the primary site for post-prandial glucose disposal. Skeletal muscle insulin resistance, leading to a reduction in insulin-stimulated glucose disposal, is often an early defect contributing to the development of type 2 diabetes.

In response to a rise in blood glucose, insulin is rapidly released from the pancreas, leading to increased glucose uptake, primarily into skeletal muscle and adipose tissue. Muscle contraction also results in a similar and rapid increase in glucose uptake into the working muscle. Contraction-activated glucose uptake does not utilise the same molecular pathways as insulin, and occurs also in the absence of insulin, making this pathway an attractive target for bypassing insulin resistance.

'While exercise-induced muscle growth is perhaps a more intuitively appreciated response to muscle use, it is the exercise-mediated changes in the capacity for substrate metabolism and insulin sensitivity that probably have the more important implications for overall health'



Some of the changes noted in skeletal muscle in response to exercise.
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INSULIN-INDEPENDENT GLUCOSE UPTAKE

Uncovering the molecular mechanisms that mediate this insulin-independent glucose uptake has been the focus of much recent research, and has led to the identification of a number of different pathways, with the most emphasis being placed on activation of AMP-dependent protein kinase (AMPK). As the muscle performs work and consumes ATP, the ratio of AMP to ATP increases in the muscle, which leads to activation of AMPK. Activated AMPK inhibits energy-consuming biosynthetic and anabolic pathways, while increasing glucose uptake and promoting β-oxidation of fatty acids within the mitochondria, thus serving to restore cellular energy balance. Targeted activation of the contraction-mediated pathway to glucose uptake is a potential strategy to promote glucose uptake into insulin-resistant muscle.

In response to training, i.e. several bouts of repeated exercise, skeletal muscle adapts to increase the number of glucose transporters and number of mitochondria, thus facilitating both the uptake of glucose and the rapid generation of ATP, to meet increased demands.

ADDITIONAL PATHWAYS

Activation of AMPK mediates some of the muscle remodelling noted in response to exercise training. However, several other molecular pathways are known to play important roles in both the acute and chronic response to exercise. These include (amongst others) contraction-mediated activation of stress kinases, changes in redox balance and reactive oxygen species, and pathways responding to changes in intracellular Ca^{2+}.

A recent analysis of the human exercise-activated muscle phosphoproteome has provided a more unbiased snapshot of which proteins are phosphorylated in response to muscle work,[6] and further analysis of some of the molecules identified should provide an insight into previously unknown exercise-activated pathways.

HOW MUCH EXERCISE IS EFFECTIVE?

While training leads to persistent effects in skeletal muscle, even one single bout of exercise leads to an enhancement in skeletal muscle insulin sensitivity. This phenomenon is probably most sharply appreciated by people with insulin-dependent (type 1) diabetes, who need to reduce their insulin doses after performing exercise. The enhanced insulin sensitivity persists for several hours post-exercise and, although the precise mechanisms that mediate this effect are less well explored, there is evidence

that activation of AMPK may also play an important role in this effect of exercise.

EFFECTS ON OTHER ORGANS

In addition to local changes within the exercising muscle itself, the contracting muscle generates factors secreted into the circulation with potential to alter the metabolism and function of other organs. For example, brain-derived neurotrophic factor increases in skeletal muscle in response to exercise[7] and has been implicated as a potent mediator of exercise-dependent enhancements in learning and memory. Recent evidence also indicates that exercise training alters muscle enzymes that directly modulate circulating levels of kynurenine metabolites to protect from stress-induced depression.[8]

Numerous other factors have been described which are released from muscle in response to exercise, ranging from hormones to cytokines to microRNAs. However, the nature of the precise signals produced, and the subsequent target tissues, remain to be fully explored.

FACILITATING THE BENEFITS OF EXERCISE

While unravelling the molecular machinery that remodels muscle in a way to promote overall health may lead to new therapeutic insights, a separate challenge is encouraging better exercise habits in the population. Given that lack of time is the most common explanation for failure to exercise, identification of the most beneficial and time-efficient form of exercise should be valuable.

Clearly, not all people respond in the same way, or with the same magnitude, to any given exercise intervention, and a proportion of people have disappointing clinical outcomes even when the exercise appears to have been adequately performed.[9] Careful analysis of the exercise response at a molecular level in high as well as low responders will give insights into the relative roles of different exercise-activated molecular pathways, and may be able to inform personalised exercise intervention programmes to ensure maximum benefits.

It is likely that exercise low-responders are over-represented amongst people developing diseases linked to lack of exercise. Since this population is likely to also include people who are less able to exercise, finding effective pharmaceutical exercise mimetics will be helpful, although to date this has been challenging. In the meantime, identifying the most effective type of training programme for each person should improve the efficacy of exercise interventions, and lead to important public health benefits.

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STUDYING TISSUE-SPECIFIC METABOLIC PHYSIOLOGY IN HUMANS

WRITTEN BY LEANNE HODSON AND FREDRIK KARPE

It is often a challenge to undertake human studies of metabolic physiology specific enough to inform us about organ or tissue function. For example, as the transition from fasted to fed state reflects key adaptations to sustain life, there can be substantial change in the flux of metabolic substrates. Indeed, in some organs, a complete shift in the preference for metabolic substrate may occur. Thus, studying human organ/tissue metabolism in the fasted state may demonstrate only one facet of metabolic physiology.

Here, we describe methods we have used to enhance understanding of human tissue-specific metabolism, focusing in particular on adipose depots.

ARTERIO-VENOUS (A-V) BLOOD SAMPLING

This is a classic method of isolating an organ as a metabolic system. It can be highly informative for certain organs, but hard to apply to systems where sampling is difficult or when the organ has cellular or metabolic heterogeneity. The A-V technique is based on the Fick principle, and has been used to study leg and forearm (approximating to skeletal muscle)[1–3] and heart,[4] with hepatic vein sampling used to study the liver.[5,6] Sampling of the inferior epigastric vein and the saphenous vein has been used to study subcutaneous abdominal and femoral adipose tissue respectively.[2,3,7–10]

Where arterial blood cannot be obtained, the arterialised-venous (heated hand) technique has been used. The potential effects of body temperature and skin blood flow must be taken into account in this method, and it may be unsuitable when studying a tissue's oxygen consumption.[11,12] The

position of venous catheters also needs careful consideration as some veins, such as the femoral vein, receive blood from leg muscles as well as adipose tissue and skin.[12]

The A-V difference technique, combined with measuring the blood flow of the organ/tissue of interest, allows for measurement of net flux of a substance, along with the clearance of a substance by the tissue. We have used A-V difference methodology, with selective venous catheterisation of subcutaneous abdominal adipose tissue and forearm skeletal muscle, in studies with stable isotopes to describe the metabolic characteristics of these tissues after an overnight fast and after a mixed test meal.[3] Chylomicron (dietary/exogenous) and very low-density lipoprotein (VLDL; endogenous) triacylglycerol (TG) were both cleared across adipose tissue and muscle, with the fractional extraction of chylomicron-TG being notably greater than that of VLDL-TG.[3]

'Rapid progress in imaging is providing less invasive techniques for tissue-specific metabolic physiology studies'

Using A-V difference across subcutaneous abdominal adipose tissue and feeding mixed meals 5 hours apart, we found the adipose tissue of lean males was more metabolically active over a 24-hour period than that of abdominally obese subjects.[13] In particular, abdominally obese males stored a significantly lower proportion of dietary fat in subcutaneous abdominal adipose tissue than did lean men, which may increase the amount of fat stored in liver and skeletal muscle.[13]

We have also used A-V methodology to describe the metabolic characteristics of subcutaneous abdominal and gluteofemoral adipose tissue in the fasting and postprandial states[14] and after adrenergic stimulation.[15] We found distinct metabolic differences in fatty acid flux and blood flow between the fat depots, with the gluteofemoral depot being more metabolically inactive compared with the abdominal depot.[14,15]

USING METABOLIC TRACERS

Metabolic tracers (stable and radioisotopes) provide the opportunity to specifically study tissue metabolism or probe specific metabolic pathways. Factors to be considered include the method of delivery, the natural abundance of the tracer, the metabolic handling of the tracer, the molecules being labelled, background meal effects and the time between repeat study visits.

IMAGING MODALITIES

Rapid progress in imaging is providing less invasive techniques for tissue-specific metabolic physiology studies. Metabolic imaging modalities include positron emission tomography (PET), magnetic resonance imaging/spectroscopy (MRI/S), computed tomography (CT) and ultrasound (US). Along with assessing substrate metabolism, imaging modalities can measure organ-specific perfusion (PET), tissue density and type of adipose tissue (CT), ectopic fat deposition, metabolite content and blood oxygenation levels in the brain (MRI/S) and liver stiffness/fat (US).[16]

Tracers have been used in combination PET and MRI/S to investigate fatty acid and glucose metabolism *in vivo* in humans. For example, by feeding individuals a meal containing ^{13}C-fatty acids and then measuring the ^{13}C signal in the liver with MRI/S at intervals postprandially, the flux of dietary fatty acids across the liver was found to be notably slower in individuals with high compared with low liver fat content.[17]

Hyperpolarised MRI (HP MRI) is an emerging technique allowing detection of ^{13}C-enriched molecules with a significantly increased signal compared with conventional techniques. HP MRI will make it possible to follow single and multiple metabolic pathways using single or multiple hyperpolarised probes, along with tracing the real-time conversion of substrate to its metabolic products,[18] but the technical platforms are expensive and experience in humans is limited.

PET is an alternative non-invasive imaging approach, which has been used to investigate organ- or tissue-specific metabolism. This has typically been undertaken in the fasting state. Using PET and ^{11}C-palmitate, obese subjects were shown to have increased hepatic fatty acid oxidation, with no difference in hepatic fatty acid uptake and esterification rates, compared with non-obese controls in the fasting state.[19]

More recently, the metabolic probe ^{18}F-FTHA and PET were used to study metabolic changes in adipose tissue in obese individuals before and after weight loss.[20] After weight loss, there was no change in the uptake of non-esterified fatty acids into visceral and subcutaneous abdominal adipose tissues, but uptake by femoral adipose tissue was significantly decreased.

The short half-life of the radioisotopes suitable for PET restricts this technique to studying metabolic pathways with a short time frame, such as glucose or fatty acid uptake. Metabolic conversions, such as glycolysis or fatty acid oxidation, cannot be studied. A final consideration is that PET can detect incorporation of radiolabelled tracers into a tissue but cannot distinguish the parent compound from the formed radiolabelled product.[18]

In summary, studies of tissue-specific metabolic function have classically relied on complex A-V balance techniques, preferably using labelled metabolic tracers. However, novel metabolic imaging techniques are creating new opportunities for such studies in humans.

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Lambeth Country Show

CALL FOR VOLUNTEERS!

SATURDAY 16 JULY 2016

We are looking for members to volunteer on the Society for Endocrinology stand to chat to the public about hormones on Saturday 16 July at Lambeth Country Show – a traditional country show with a twist!

Hands-on activities will include testing glucose levels in an imitation blood sample and learning about circadian rhythm by creating your own body clock. It promises to be a great day out and a fantastic opportunity to increase hormone awareness as well as improving your communication skills!

To volunteer or for more information, email Joanne Stubbs at **joanne.stubbs@endocrinology.org**.

"I have a passion for science which I want share with younger children to get them inspired.

I usually find that I communicate my research to my peers so it's nice to explore other ways of getting concepts across.

A massively rewarding way to spend a weekend..."

DO BUILT ENVIRONMENTS SHAPE OUR HEALTH?

WRITTEN BY LOUISE FOLEY, CORNELIA GUELL, JENNA PANTER & DAVID OGILVIE

Physical inactivity is a major contributor to morbidity and mortality around the globe, not only through an increased risk of diabetes, but also through heart disease, stroke, cancer, dementia, depression and arthritis. Inactivity is estimated to account for 9% of premature deaths worldwide.[1]

This knowledge, however, does not seem to have been translated into effective action. More than a third of adults in the UK report not doing the minimum amount of physical activity recommended for health by the Chief Medical Officers, despite a range of campaigns aimed at educating or cajoling the public into getting active. Evidence suggests these individually targeted approaches often produce modest and short-lived improvements at best – an underwhelming result given the magnitude of the challenge.

Most of the world's population now live in cities, with the global urban population expected to grow by nearly 2% per year until 2020. There is good evidence that the urban form influences physical activity or inactivity: in particular, whether people use active or motorised forms of transport. This suggests that changing the built environment could produce broader, more sustained effects on physical activity across the population than individually targeted approaches. Research suggests that changes such as introducing traffic calming or road user charging, or building dedicated walking and cycling routes, can increase levels of walking and cycling for transport, and thus physical activity. However, strong evidence to guide practice has been slow to emerge.[2]

SEEKING REAL WORLD ANSWERS

The lack of evidence reflects the difficulty of conducting research in this emerging field at the intersection of transport and health, which draws scientists out of the sterile confines of the laboratory into the messy world of real lives and political agendas. Robust science to understand the effect of changes in the built environment on changes in behaviour and health depends on using creative methodological approaches to extend the repertoire beyond the stalwart of clinical research, the randomised controlled trial (RCT).

RCTs entail randomised controlled comparisons over time, and are generally agreed to be the best way to identify whether a treatment causes an effect. However, real world 'treatments' which have the potential to affect health, but which are not amenable to randomisation, happen all the time. Examples include banning smoking in public places, alcohol taxation or congestion charging. The effects of these 'treatments' can and should be investigated, not least because the underpinning policy should be guided by evidence. Recent Medical Research Council (MRC) guidance calls for the use of natural experimental studies, typically involving non-randomised controlled comparisons over time, to generate stronger evidence of the effects of environmental and policy changes.[3]

'…changes such as introducing traffic calming or road user charging, or building dedicated walking and cycling routes, can increase levels of walking and cycling for transport, and thus physical activity'

RESEARCH IN PRACTICE

As part of the Centre for Diet and Activity Research at the MRC Epidemiology Unit in Cambridge, our Physical Activity and Public Health research programme has used the natural experimental approach to evaluate the effects of new transport infrastructure on active travel and physical activity. This has included the assessment of a new 'guided busway' in Cambridge, comprising a new bus network, park and ride sites and a traffic-free path for pedestrians and cyclists, as well as new dedicated cycling and walking routes in other UK cities, and a new urban motorway built through a residential area of Glasgow.

'This body of work is already informing transport and urban planning policy, ultimately aiming to help transform our cities into places that support physical activity and health for all'

The first two studies have shown that building new walking or cycling infrastructure facilitates these behaviours in those living nearby.[4,5] In the busway study, the effects of the new provision were particularly pronounced amongst those who were previously the least active – the group with the most potential health gain from taking up more activity. Findings from the motorway study, which investigates effects on travel, physical activity and well-being, are expected to be released later in 2016.

ADDRESSING LIMITATIONS

A key limitation of natural experimental studies is that the lack of randomisation increases the possibility that comparison groups differ in ways that affect their response to treatment, which might bias estimates of the treatment effect. Therefore, all three studies were carefully designed to ensure that comparison groups were as similar as possible apart from their exposure to the intervention, to minimise this inherent risk of bias.

This entailed comparing people who lived nearer to or farther from the new infrastructure, and accounting for differences in individual, geographical or household characteristics. Additionally, in the motorway study, three geographical areas were carefully delineated around the new motorway, an existing motorway built decades earlier, and an area with no motorway, to provide additional comparisons.

Over time, these studies – conducted in a range of contexts, including people from various socio-economic backgrounds, and examining different types of transport infrastructure – will allow us to draw more generalisable conclusions about the likely health effects of changing particular aspects of the urban environment. This body of work is already informing transport and urban planning policy, ultimately aiming to help transform our cities into places that support physical activity and health for all.

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The Centre for Diet and Activity Research, which is a partnership between the University of Cambridge, the University of East Anglia and the MRC, is one of five Centres of Excellence in Public Health Research funded through the UK Clinical Research Collaboration (UKCRC). The Physical Activity and Public Health research programme is a core programme at the MRC Epidemiology Unit.

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OPINION

SHOWBIZ, STARDOM … AND INTERCELLULAR SIGNALLING?

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

Reading of the soon-to-be-released maths biopic 'The Man Who Knew Infinity', I was reminded of Tony Coll's column in *The Endocrinologist*, issue 116, which described his enjoyment of 'X+Y' – a love story between an 'awkward and troubled prodigy' and his favourite sums.

To my continued amazement, the film industry seems convinced that mathematics makes for good movies. There have been recent biopics of Alan Turing and Stephen Hawking, and, further back, 'A Beautiful Mind', as well as fictions including 'Good Will Hunting', 'Proof' and 'Pi'. Who would have thought dramatically scribbling equations on blackboards and conversing with imaginary friends was so entertaining?

> ***'Perhaps the least of the cinematic crimes of "Hansel and Gretel: Witch Hunters" is its inaccurate depiction of Hansel's diabetes'***

Hollywood also needs chemists (to make suits out of indestructible fabric and to formulate drugs and poisons) and physicists (to invent time machines, gurn maniacally and make ill-considered, housefly-accompanied teleport jumps).

In general, biologists too are well represented on the big screen. The discoveries of natural selection and DNA have been dramatised on TV and stage and in film. Marine biologists traditionally provide useful advice on how to risk-manage man-eating sharks or a kraken, and entire clades of palaeontologists have been inspired by the various 'Jurassic Park' films.

Primates that remain in the rainforest can rely on heroic zoologists for their protection, but those in laboratories tend to suffer at the hands of white-coated experimentalists. In '28 Days Later', their anguish is compounded by such deathless dialogue as 'To cure, you must first understand…', which seems to offer little consolation to the chimp in question.

So, more importantly, where are the endocrinologists? Diabetes plays a supporting role in many films. Poor glucose control finishes off Julia Roberts in 'Steel Magnolias' and Judi Dench in 'Chocolat'. Film makers often use the need for insulin to add urgency to plots, as in 'Con Air' and 'Panic Room'. Perhaps the least of the cinematic crimes of 'Hansel and Gretel: Witch Hunters' is its inaccurate depiction of Hansel's diabetes (aetiology: eating too many sweets at the original witch's gingerbread cottage).

My particular favourite is the late-80s horror movie 'Warlock', in which the diabetic heroine kills Julian Sands for crimes against God (and over-acting) by injecting him with salt water using her insulin syringes. (Warlocks, as you are no doubt aware, react badly to salt, perhaps reflecting some defect in the warlockian renin-angiotensin system.)

But none of these movies actually feature a heroic (or villainous) endocrinologist. True, there aren't many endocrine emergencies. 'Thyroid Storm' is a good name for a Scandinavian black metal band, but it's difficult to hang a movie on. 'Negative Feedback' sounds like a decent thriller, but the plot summary ('…and subsequently homeostasis is maintained') lacks tension.

Movies should reflect the audience that watches them, including endocrinologists. So who will step up and make the movies we all want to see: 'Ernest Starling and the Chamber of Secretin', 'From Dusk till the Dawn Phenomenon', 'There will be Blood … borne Signalling Molecules'…?

KEVIN MURPHY
Science Committee correspondent

JOURNAL SHOPPING: CAREERS, COMPETITION AND COUNTDOWNS

WRITTEN BY SAFFRON WHITEHEAD

The old adage 'publish or perish' still persists, but how easy is it to get into print these days? Despite the increased number of journals, especially open access publications that boast of rapid review and publication times, it seems to be increasingly difficult and lengthy, particularly in the case of high impact journals to which we all aspire.

The problem is that career progress, promotions, grants and REF (Research Excellence Framework) grading depend on track records which use (amongst other things) bibliometrics. Both numbers of publications and impact factors of journals are scrutinised.

When I began publishing in the mid-1970s, none of my papers were rejected, and referees usually came back with 'minor revisions' required. There was no question of paying for publication. But things have changed, particularly in the last decade.

JOURNAL SHOPPING

I know I am not the only one who has done 'journal shopping', starting off with submission of one's paper to an appropriate journal with the highest impact factor. Rejection may be without review. Then one tries the next one down the line, and on it may go.

Perhaps on the third or fourth attempt (by now the impact factor has dropped considerably and authors are becoming demoralised!) there seems to be a bite on the hook. The submission is neither accepted nor rejected but, based on the reviewers' comments, major revisions are required by the Editor before resubmission. This can mean more months of further experiments and a rewrite, though often with exactly the same conclusions as one's original submission. However, even having addressed all the reviewers' questions, a paper can still be rejected. So a year or so can elapse since the original submission.

A CLOSER LOOK AT REVIEW TIMES

Apart from these potential delays, other factors may explain the lengthening process of publication. A fascinating news feature by Powell in *Nature* quotes the results of different analyses.[1]

High and very low impact journals have the longest time from submission to review (around 130 to >150 days). For example, over the past decade the median time for *Nature* has increased from 85 days to around 150 days, and that for *PLOS ONE* from 37 to 125 days. One analysis showed that times for the whole PLOS family of journals have roughly doubled from 50–130 days to 150–250 days!

DATA PER PAPER

More interesting is that the amount of data per paper has increased considerably. Powell's analysis was based on the number of panels of experimental figures in three high impact journals: *Cell*, *Nature* and *Journal of Cell Biology*. In 1984, the number of panels was 10–18 but by 2014 it was 20–40. These increased figures were also correlated with an increase in the number of authors on each paper.

Does this reflect the increased demand for experimental data or the need to get doctoral and post-doctoral students to increase their publications to help with their careers? Many a time I have had intercalated students ask if their project work would be published because it would help with their placements. So pressure is there at all levels.

When I started my career, there were usually only two or three authors to each paper. The main researcher's name came first with the name of the funder or supervisor second or last. Any middle authors were considered a relatively insignificant piece of the jigsaw puzzle. We all knew our place! Well, except in *Journal of Physiology* that insisted authors were listed alphabetically. I suppose that took the hierarchy out of the system but I still remember my first publication when I put my name last – I had made it as a supervisor of research!

'I suspect the increasing number of submissions results from journal shopping and contributes to the lengthening time of the review process'

THE MARCH OF TECHNOLOGY

What about digital printing? Well, the good news is that time from acceptance to publication has halved since the early 2000s to a median time of 25 days, and many journals now put preprints online after acceptance. This contrasts to the lengthening time of the review process, which I suspect is partly due to the increasing number of submissions resulting from 'journal shopping'. According to Veronique Kiermer, executive editor of *PLOS ONE*, the volume of submissions has risen from 200 in 2006 to 30,000 a year today. In 2015 the journal used 76,000 reviewers.

JOURNALS CLOSE TO HOME

So, how do the Society's journals fare? According to Simon Laurenson, Operations Manager for Bioscientifica, the submissions for *Journal of Endocrinology*, *Journal of Molecular Endocrinology* and *Endocrine-Related Cancer* were 1,500 in 2015, review times around 100 days, acceptance rates about 20% and publication was around 40 days after acceptance. For the open access publication *Endocrine Connections*, submissions were lower and acceptance rates higher (33%).

The competition for publication in the highest impact factor journals is now fierce, as it is for research grants. This all takes time away from research, which is the basis of funding and publications. Perhaps this is one reason why researchers go for the open access journals where the quality of science may be lower but acceptance rate higher and publication times quicker – though this option is more costly.

We all love our name in print and I still remember my first publication (no online publishing then, but 50 free offprints sent in the post!). There I was – over 40 years ago – in a scientific journal: name first, supervisor second. As they say, 'times they are a-changing'.

SAFFRON WHITEHEAD
Emeritus Professor, St George's University of London

REFERENCE

1. Powell K 2016 *Nature* **530** 148–151.

GENOMICS IN MAINSTREAM ENDOCRINOLOGY

WRITTEN BY CHRISTINE MAY, NEIL GITTOES & TREVOR COLE

Our genetic constitution is a key factor contributing to our individual risk and prognosis for many medical conditions. Some disorders already have a well-established genetic cause: for example, the receptor tyrosine kinase (*RET*) proto-oncogene and multiple endocrine neoplasia type 2. In contrast, in other conditions we have yet to understand the full implications of genetic contributions.

Historically, we have taken a family history to look for familial patterns in conditions, but this relies on relatives communicating their medical history within the family, and will be uninformative for cases which are apparently sporadic.

We have become increasingly aware that it is rarely a single gene that causes a disease. Multiple factors including our genome (the collection of genes and the DNA between the genes) and environmental factors all play a role. Genomics is the discipline encompassing the study, sequencing and analysis of the genome and interactions between genes and the application of this knowledge to medicine. Pharmacogenomics is the customisation of medical therapies to the patient's individual genetic makeup.

The Human Genome Project, which took 13 years, completed the sequencing of the reference genome in April 2003.[1] This remains one of the largest scientific ventures in history. The subsequent genomic revolution has not only led to advances in medicine but affects many other areas of our lives, e.g. veterinary sciences and agriculture. Genetic research has since progressed to the point where rapid sequencing of DNA is now technically achievable in a single day, albeit rarely applicable in routine practice.

IMPACT ON CURRENT PRACTICE

Within our specialty of diabetes and endocrinology, you do not have to look far to come across genomics and pharmacogenomics already embedded in our current clinical practice.[2]

For example, we know that patients diagnosed with maturity onset diabetes of the young due to a *HNF1A* mutation are extremely sensitive to sulphonylureas.[3] Investigation of the underlying aetiology of medullary thyroid cancer identifies that up to one-third of cases may have a germline mutation, and this affects the information we give to the individual and their family for screening and further management. Likewise, 10–20% of apparently isolated phaeochromocytomas and paragangliomas have a germline mutation in one of nine identified genes.

THE 100,000 GENOMES PROJECT

The 100,000 Genomes Project is underway, aiming to sequence the genetic code of patients and their family members, looking at rare inherited disorders, specific malignancies and infectious diseases.[4] The first group typically will have none of the known genetic causes on testing or be very heterogeneous, with too many different causative genes involved for testing to be practical in routine service. The table lists the diabetes and endocrinology conditions that are eligible for the project, as listed in the project information in January 2016.[5]

The project's aim is to identify pathogenic genetic sequence changes leading to more accurate diagnoses, personalised treatments and more predictable outcomes, changing the application of genomic medicine. Clinicians within the NHS can identify patients who may be eligible and refer them to their local genomic medicine centre. This is available through the Genomics England website,[4] which also includes a link to enable an application to be made to nominate a new rare disease (incidence not greater than 1 in 2,000).[5]

DRAWING CONCLUSIONS

Within our specialty, we already have many multidisciplinary clinics which manage patients jointly with genetics teams. Further advances in genomics are helping with new diagnostic, investigatory and therapeutic strategies in many conditions. In the future, all clinicians will need to become increasingly comfortable with embedding genomics into our day-to-day clinical practice, to tailor patients' management plans to deliver more personalised medical care.

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NEIL GITTOES
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TREVOR COLE
Birmingham Women's Hospital, Birmingham Health Partners

*The authors are all members of the Genomics in Mainstream Medicine Working Group (**http://bit.ly/1Takn6y**).*

The 100,000 Genomes Project: ***www.genomicsengland.co.uk***
PHG Foundation: ***www.phgfoundation.org/education***
Health Education England (Genomics Education Programme): ***www.genomicseducation.hee.nhs.uk***

REFERENCES

1. Tripp S & Gruber M 2011 *Economic Impact of the Human Genome Project* http://bit.ly/1VWRTDE.
2. May CJH *et al.* 2015 *Genomics in Mainstream Medicine: Endocrinology, Diabetes and Genomics* www.phgfoundation.org/file/17032.
3. International Diabetes Federation 2011 *Global IDF/ISPAD Guideline for Diabetes in Childhood and Adolescence* http://bit.ly/1SD73HL.
4. Genomics England 2015 *The 100,000 Genomes Project* www.genomicsengland.co.uk/the-100000-genomes-project.
5. Genomics England 2015 *Nominating a Disease for Inclusion in the 100,000 Genomes Project* http://bit.ly/1TAVxfY.

Diabetes and endocrine conditions eligible for inclusion in the 100,000 Genomes Project.[5]

Endocrine disorders	Adrenal disorders	• Congenital adrenal hypoplasia
	Disorders of calcium homeostasis	• Familial or syndromic hypoparathyroidism
	Growth hormone disorders	• Intrauterine growth restriction and IGF abnormalities
	Disorders of unusual phenotypes	• Familial young-onset non-insulin-dependent diabetes • Hyperinsulinism • Neonatal diabetes (diagnosed <6 months) • Diabetes with additional phenotypes suggestive of a monogenic aetiology • Insulin resistance (including lipodystrophy) • Multi-organ autoimmune diabetes
	Obesity syndromes	• Significant early-onset obesity ± other endocrine features and short stature
Tumour predisposition disorders	Breast and endocrine	• Familial breast cancer • Multiple endocrine tumours • Neuroendocrine tumours: phaeochromocytoma and paraganglioma • Parathyroid cancer
Skeletal disorders	Skeletal dysplasias	• Osteogenesis imperfecta • Multiple epiphyseal dysplasia • Chondrodysplasia punctata • Thoracic dystrophies • Stickler syndrome

Better get to Brighton!
SfE BES 2016

The Society for Endocrinology BES conference is the largest meeting of endocrine professionals in the UK, providing a forum for scientists, clinicians and nurses to come together and exchange ideas.

HERE'S WHAT YOU CAN EXPECT

70 YEARS OF ENDOCRINOLOGY ...

2016 is a milestone year for the Society, as we celebrate 70 years of advancing endocrine education, research and practice. Our annual conference will provide the perfect opportunity to recognise how members have helped transform endocrinology over the past seven decades, and to look ahead to the future directions for our field.

10 PLENARY LECTURES ...

including:

- Professor Sir Stephen Bloom's Jubilee Medal Lecture: '*Gut and money, customer shrunk*'
- Professor Henry Kronenberg's Transatlantic Medal Lecture: '*Parathyroid hormone: builder and destroyer of bone*'
- Professor Jason Carroll's Society for Endocrinology Medal Lecture: '*Understanding oestrogen receptor gene regulation in breast cancer*'

12 SYMPOSIA ...

on cutting edge research and practice, such as novel approaches to endocrine neoplasia, advances in the genetic understanding of endocrine disease, and new frontiers for vitamin D.

9 'MEET THE EXPERT' SESSIONS ...

exploring hot topics such as endocrine disruptors, the late effects of cancer treatment, and how to effectively treat endocrine patients in sport.

3 'FUTURES' AND 'SKILLS' SESSIONS ...

providing guidance on how to progress to the next stage in your endocrine career. This year you'll be able to get tips on how to avoid common pitfalls in your grant proposals, how to maximise your chances in fellowship applications, and how to find out everything you need to know about the Specialty Certificate Exam.

1 DEBATE ...

looking at the arguments for and against using prednisolone as the first line treatment for glucocorticoid replacement in adrenal insufficiency.

2 LOUNGES ...

for Nurses and Early Career Endocrinologists, providing space to network with colleagues.

1 CONFERENCE DINNER ...

an awards ceremony, and an exciting variety of other social activities to allow you to catch up with colleagues, old and new.

To view the full conference programme, and register your place, visit **www.endocrinology.org/meetings/2016/sfebes2016**. We look forward to welcoming you to Brighton!

ABSTRACT DEADLINE:
15 June 2016

Bone and Calcium ENDOCRINE NETWORK

WRITTEN BY DUNCAN BASSETT & COLIN FARQUHARSON

The endocrine system plays a critical role in the regulation of skeletal development, maintenance and repair, and is essential for mineral homeostasis.

Disruption of endocrine signalling in vitamin D deficiency, parathyroid, thyroid, pituitary and adrenal disease and following gonadal failure leads to abnormalities of skeletal growth, remodelling and mineralisation. The resulting diseases are major healthcare challenges and include rickets, osteomalacia, primary hyperparathyroidism and osteoporosis.

Recent advances in endocrinology, driven by a combination of mouse genetics, integrative physiology and clinical observations, have established bone as a novel endocrine organ regulating phosphate homeostasis (fibroblast growth factor 23; FGF23), glucose metabolism (under-carboxylated osteocalcin) and bone formation (sclerostin). Whilst major advances have been made in understanding the pathophysiology of skeletal disease and translating this into novel treatments, many challenges remain.

To bring like-minded basic science and clinical researchers together, and encourage cross-disciplinary research, the Society for Endocrinology has established dedicated forums in key areas of endocrinology: namely Endocrine Networks. Specifically, the Bone and Calcium Endocrine Network (BACN) has been established to enable Society members with an interest in skeletal physiology and metabolic bone disease to come together, share research ideas and best clinical practice, and find solutions to the challenges they face.

INITIAL ACTIVITIES

The first meeting of BACN took place at the Society for Endocrinology BES conference 2015 in Edinburgh and, whilst it is still early days, BACN members have already had an impact.

- BACN members have contributed to NHS England policy by consulting on the 'Clinical Commissioning Policy Proposition: Cinacalet for complex primary hyperparathyroidism'.
- They have also been involved in the British Society for Rheumatology nationwide survey to determine the frequency and nature of 'Individual Funding Requests' for the treatment of patients with skeletal disease.
- Members have facilitated liaison between the Society for Endocrinology's Clinical Committee and BACN to investigate new clinical research opportunities in asymptomatic primary hyperparathyroidism.

FUNDING OPPORTUNITIES

To encourage cross-institutional and collaborative research, network convenors can apply for an Endocrine Network Research Grant from the Society for Endocrinology (see **http://bit.ly/23NKjiW**). These grants, of up to £5,000, focused on Network activity, can allow for pump-priming successful bids for larger scale national or European funding opportunities including those from the National Institute for Health Research, Medical Research Council, Wellcome Trust and Horizon 2020.

'Recent advances in endocrinology have established bone as a novel endocrine organ regulating phosphate homeostasis, glucose metabolism and bone formation'

The Society's Themed Scientific Meeting Grant, open to all members, provides additional funding opportunities (of up to £10,000) to host short focused scientific meetings, to encourage community building between our younger and more experienced members (see **http://bit.ly/1VpE9R3**).

PLANS FOR THE FUTURE

BACN also has a vital role in ensuring that the Society for Endocrinology BES conference programme contains world-leading basic and clinical science in skeletal physiology and metabolic bone disease. This will be achieved by engaging with Network members to identify international leaders in the field for Society prizes and plenary lectures, as well as speakers for symposia and Meet the Expert sessions. Representation of BACN on the Society's Clinical, Science and Programme Committees will ensure that the field continues to be strongly represented at the annual conference.

Over the forthcoming year, we will establish a BACN web page to develop and establish the Network as a forum and influential mouthpiece for its members. We will also facilitate and advertise BACN meetings at other national and international meetings frequently attended by BACN members, and promote the Network to other related learned societies, such as the Bone Research Society.

We are very keen to hear your suggestions for how the BACN can help you, as well as increasing the profile of bone and calcium as an endocrine specialty.

DUNCAN BASSETT & COLIN FARQUHARSON
Network Leads

*Find out more at **www.endocrinology.org/endocrinenetworks** or contact **debbie.willis@endocrinology.org**.*

Publishing ROUND-UP

NEW ONCOLOGY RESOURCE

Hormone-Related Cancer is a new website that brings together the latest oncology research, reviews and case reports from Society for Endocrinology journals, amongst others.

New papers will be added on a regular basis and arranged by sub-specialism, including breast, prostate, thyroid and adrenal cancers, neuroendocrine tumours, and multiple endocrine neoplasia/genetics.

Browse the latest content at **www.bioscicollections-hrc.com**.

SOCIETY JOURNAL TO PUBLISH VIDEOS

Journal of Molecular Endocrinology now offers authors the ability to publish inline videos in the online versions of research articles. Researchers who have produced moving images as part of their work can now share these with readers. For a limited time, articles featuring videos will be published Open Access free of charge. To benefit from this offer, submit by 31 December 2016 and quote 'OA VIDEO' in your cover letter.

JOURNAL OF MOLECULAR ENDOCRINOLOGY SPECIAL ISSUE: 60 YEARS OF POMC

The May issue of *Journal of Molecular Endocrinology* marks 60 years of research on pro-opiomelanocortin (POMC), celebrating the landmark research of Choh Hao Li.

The special issue has been guest-edited by Adrian Clark (picutred on the left) and Philip Lowry (on the right), who have contributed an editorial, and contains 12 thematic reviews.

JOURNALS ON TWITTER

You can now keep up-to-date with newly published articles and reviews from your Society's journals on Twitter. Don't forget: as a member of the Society, you can access all published articles free of charge!

- **@JEndocrinology**
- **@JMolEndo**
- **@EndoConnect**
- **@EndoCancer**
- **@EDMCaseReports**

Grants and Awards

2016 APPLICATION DEADLINES FOR YOUR DIARY

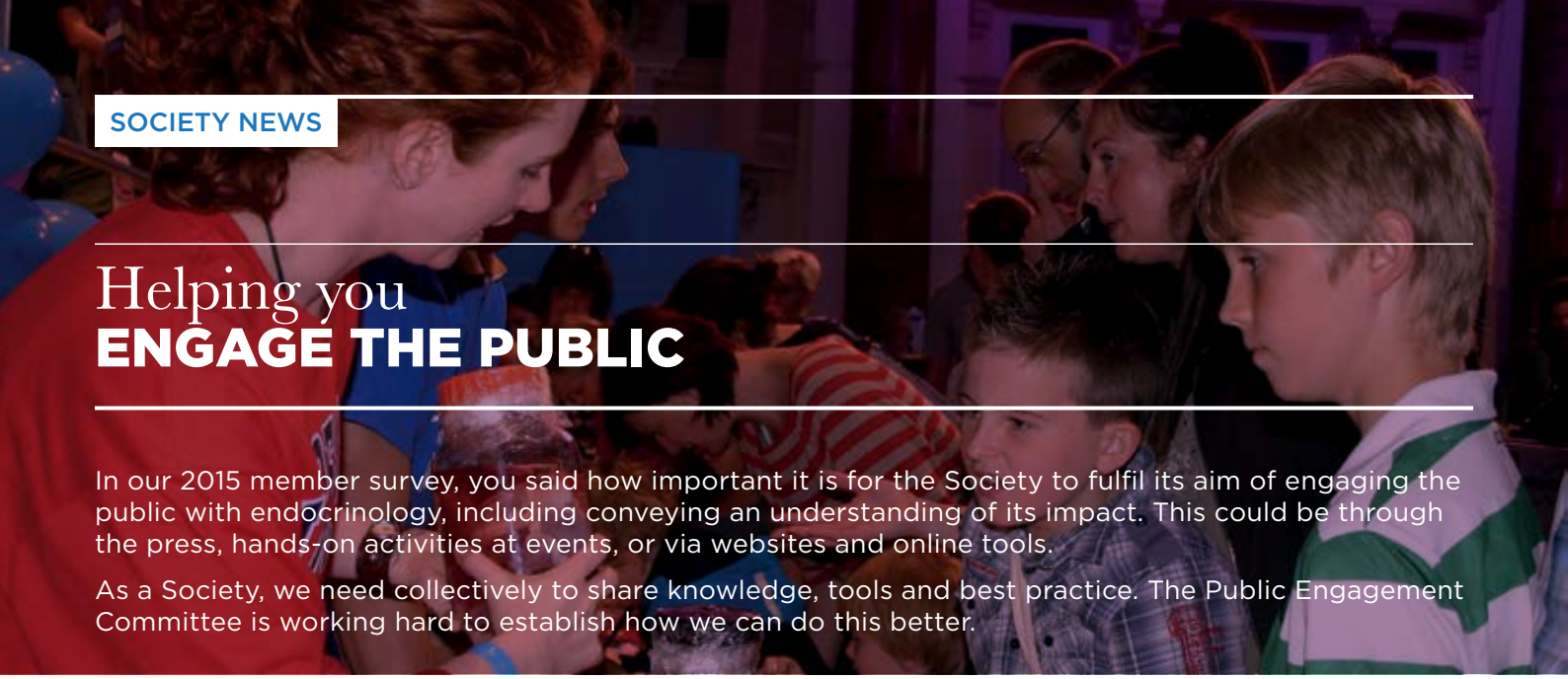
- Society for Endocrinology BES 2016 Registration Grants – **4 July**
- Undergraduate Achievement Award – **13 July**
- Travel Grants (for SfE BES 2016 or an overseas meeting ending before 15 December) – **15 August**
- Public Engagement Grants – **30 September**
- Equipment Grants – **27 November**
- Early Career Grants – **27 November**
- Travel Grants (for SfE Endocrine Nurse Update, ENDO 2017 or an overseas meeting ending before 15 March) – **15 December**

APPLY ALL YEAR ROUND...

- Practical Skills Grants
- Endocrine Network Research Grants

Find out more about the grants, awards and prizes available to Society members at www.endocrinology.org/grants

Your Society provided more than £450,000 in grants to members in 2015



Helping you ENGAGE THE PUBLIC

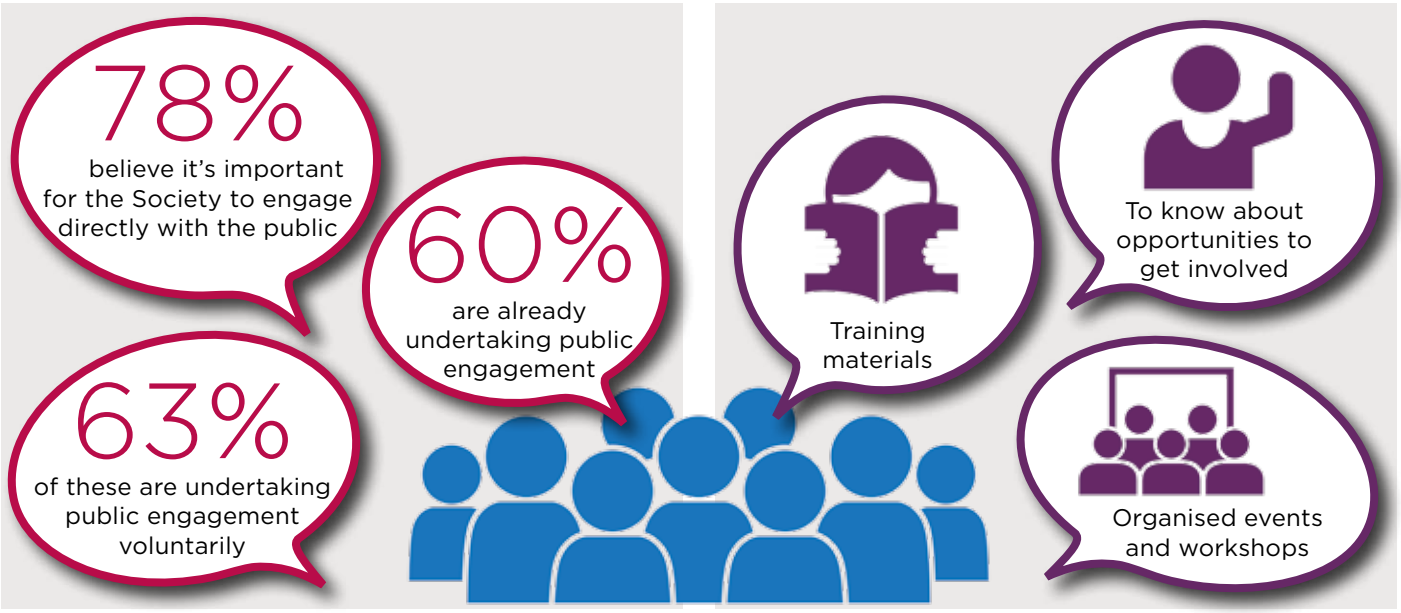
In our 2015 member survey, you said how important it is for the Society to fulfil its aim of engaging the public with endocrinology, including conveying an understanding of its impact. This could be through the press, hands-on activities at events, or via websites and online tools.

As a Society, we need collectively to share knowledge, tools and best practice. The Public Engagement Committee is working hard to establish how we can do this better.

WHAT YOU TOLD US

WHAT YOU SAID YOU NEEDED

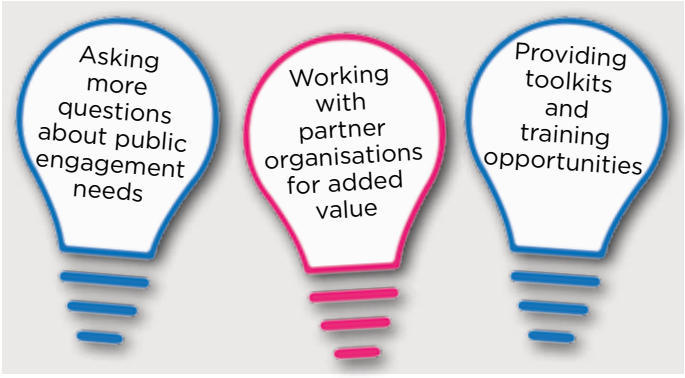
2015 member survey, 194 respondents



WE SUGGEST...

raising the profile of public engagement within the Society

enabling you to act as public engagement ambassadors



The next issue of *The Endocrinologist* will introduce you to some of the projects and practices currently being undertaken by Society members.

New partnership between **PFIZER AND THE SOCIETY FOR ENDOCRINOLOGY**

The Society for Endocrinology has agreed a new 2-year partnership with Pfizer. The agreement is the first of its kind for the Society, and is the result of more than 6 months of discussions to ensure maximum benefit to both organisations and their broader aims of advancing endocrinology.

Paul Carroll, Chair of the Society for Endocrinology Corporate Liaison Board, says:

"The partnership recognises the Society for Endocrinology's commitment to working with industry to achieve its objectives. It represents a true collaboration with an industry partner, working on joint projects for the benefit of endocrinology. Other benefits to the Society include expert advice from Pfizer to help support different areas of our business, such as digital communications.

With a dynamic global health environment, pharmaceutical companies are looking for different ways of working with learned societies, to help understand and focus on areas of greatest need for patients. This partnership is a great position from which the Society for Endocrinology can develop its sponsorship models, not only to ensure sustainability, but to work together to meet the Society's aim of advancing endocrinology research and medicine globally."

James Steed, UK Brand Lead for Endocrine Care at Pfizer, says:

"We believe "together works better" and we're delighted to be working with the Society for Endocrinology. Pfizer has been conducting research and working in partnership with those across health and life sciences for over 60 years. As well as being a leading supplier of medicines to the NHS, we are committed to collaborating with our partners across the NHS, and beyond, to tackle challenges, improve the delivery of healthcare and achieve the best health outcomes for people across the country.

The NHS is changing in response to various pressures, and the needs of our partners and the people they care for reflect this. We believe that through working in partnership, combining our skills, experience and resources, together we can tackle some of the greatest challenges facing the NHS today. The new partnership will strengthen Pfizer's relationship with the Society and ultimately improve patient care."

SOCIETY FOR ENDOCRINOLOGY CORPORATE SUPPORTERS 2016

Partner:
Pfizer

Platinum Supporter:
Bioscientifica

Silver Supporters:
HRA Pharma
Lilly

Gold Supporter:
Shire UK

Ipsen Ltd
Novartis

For more information, visit **www.endocrinology.org/corporate** or contact **amanda.helm@endocrinology.org**.

CHALLENGING THE POLICYMAKERS: VOICE OF THE FUTURE 2016

WRITTEN BY AMBER ABERNETHIE

Optimising failed experiments or collecting negative results can leave a PhD student feeling less than successful. However, after attending the recent Voice of the Future 2016 event, I came back not just with a new insight into policymaking, but also with a refreshing wider perspective on how important these aspects of science are too.

Nicola Blackwood MP, Chair of the Science and Techonology Committee, responds to questions. ©Royal Society of Biology

Voice of the Future, which I attended on behalf of the Society for Endocrinology, takes place annually at the Houses of Parliament. It enables us, as scientists, to experience how it feels to be an MP sitting in a Select Committee meeting, putting our questions to key influential policymakers.

This year, after an exciting introduction from the Rt Hon John Bercow MP (the Speaker of the House of Commons), the panel answering our questions included Professor Sir Mark Walport (the UK's Chief Scientific Adviser), members of the Science and Technology Select Committee, Jo Johnson MP (Minister for Universities and Science) and Yvonne Fovargue MP (Shadow Minister for Business, Innovation and Skills). Halfway through, we even received a video message from Tim Peake all the way from the International Space Station!

Common themes expressed by all of the panellists included the importance of inspiring more young people to continue with STEM subjects (science, technology, engineering and mathematics) after school, as well as addressing the barriers creating under-represented groups in these careers (which include women, people from disadvantaged backgrounds, individuals from minority ethnic groups, and those with disabilities). Other hot topics were how our science will be affected by the decision to stay or leave the EU, as well as by recent immigration restrictions.

I found Sir Mark Walport's views on the importance of good quality scientific data especially motivating. Hearing them from him gave me confidence that my lengthy optimisation to achieve reliable results (and the skills which I'm building in the process) are all the more worthwhile!

As well as returning to the lab with a new sense of purpose, the event gave me a fantastic insight into science policymaking, something which I now may consider as a career after my PhD. Thanks, Society for Endocrinology, for a great afternoon!

AMBER ABERNETHIE
Centre for Cardiovascular Research, Queen's Medical Research Institute, University of Edinburgh

Rt Hon John Bercow MP, Speaker of the House of Commons, introduces Voice of the Future. ©Royal Society of Biology

THE SWEET TASTE OF SUCCESS: FIRST UK NATIONAL UNDERGRADUATE ENDOCRINOLOGY CONFERENCE

WRITTEN BY LISA AKYOL & PHILIPPA BOOTHROYD

2015/16 saw the formation of the Edinburgh University Endocrinology Society (EUES). Not content with merely setting up the Society, we decided to hold the first UK National Undergraduate Endocrinology Conference. With no footsteps in which to follow, we had to come up with our very own recipe for success.

BUILDING A TEAM

The first step? Establishing a solid team. Initially we thought one conference co-ordinator would suffice. Thankfully, we quickly realised that a team of five from different backgrounds and year groups was much more realistic. We now had the vital basis upon which to create our masterpiece, and could take on different roles, depending on our stage at university and previous experience.

So we started to add ingredients to the 'conference cauldron'. The initial mix involved arranging our venue, date and format. Fortunately our location was easy to decide, as the Medical School Building regularly holds similar events at no cost to such student organisations. The date proved trickier as few slots were available by the time we were ready to book. Settling with the end of January, we assumed that this would suit most students.

SHORT AND SWEET

Regarding the day's format, we agreed to make our first venture short and sweet. With a sprinkling of science, a measure of medicine and a healthy dose of networking for all involved, we hoped the day would be to everyone's taste.

The major issue was arranging the perfect blend of content to attract our target audience. Our perseverance and efficient usage of the committee's email paid off. Using our student and staff connections, we were delighted with our final four speakers. It was a pleasure to welcome Ian Russell (Chief Executive, Society for Endocrinology) to open the day's proceedings.

SPREADING THE WORD

In order to whip up some interest, strong advertising was paramount. Although emails, word of mouth and noticeboards had their merits, adding a good pinch of social media into the mix was how we drew in the bulk of our audience.

Clearly, the interest in endocrinology is far-reaching, and we were pleased to receive abstract submissions from students across the UK. Three were selected to give oral presentations, in addition to a poster presentation area.

The conference organisers.

THE DAY DAWNS

Within no time at all, 23 January 2016 was upon us. Would our months of planning and preparation pay off? The proof of the pudding was in the eating! Our three student presenters delved into various aspects of endocrinology, managing to cover all facets of the bio-psycho-social model. Our guest speakers, Colin Duncan, Jessica Ivy and Rebecca Reynolds, gave us some food for thought regarding their own specialist areas. Dr Duncan's use of the role of TV's 'Dr House' was particularly creative, as he approached clinical scenarios relating to polycystic ovarian syndrome.

Posters explored a range of topics, from reproductive biology to medical education. We were fortunate enough to have a great panel of guest judges to help us choose the recipient of each award. Thanks to the skills of the committee's sponsorship convenor, prizes included a journal subscription from the Society for Endocrinology, and book vouchers from Blackwell's bookshop.

The icing on the cake came in the form of a delicious spread from the resident catering company. The coffee and cupcakes provided the perfect opportunity for all attendees to mingle, and fuelled the poster presentation session in particular.

'With a sprinkling of science, a measure of medicine and a healthy dose of networking for all involved, we hoped the day would be to everyone's taste'

POSITIVE FEEDBACK

In order to build on our success, we asked all delegates to complete a quick survey following the event. It seems that all our ingredients largely worked well together, providing a fun and informative day for delegates and speakers alike.

Ideas for development include the addition of an interactive session, and consideration of travel bursaries for those further afield.

PERSONAL BENEFITS

For ourselves as organisers, the experience has been invaluable. Networking with our peers, researchers, clinicians and students outside the university has been both good fun and beneficial for us and for EUES.

The process was by no means plain sailing and, with everyone in the team on different schedules, it meant meetings and delegated tasks were tricky to arrange. However, we all feel this has greatly improved our communication, teamwork and time management skills – vital ingredients in any career path.

So, looking back, what is the perfect recipe for a successful conference? Start early, get a date to suit your target audience, make the most of the contacts you have and above all, assemble a top-notch team ready to rise to the challenge. The cherry on top? Serving up a good cup of coffee!

LISA AKYOL
4th year medical student, University of Edinburgh

PHILIPPA BOOTHROYD
3rd year medical student, University of Edinburgh

Lisa and Philippa were part of the conference organising committee along with David Henshall, Rachel Stewart and YuJing Ooi. You can find out more about EUES at ***euesoc.wix.com/eues*** *or* ***http://bit.ly/23NOrzr****.*

LISA SHEPHERD

NURSE COMMITTEE CHAIR

Following on from the spring issue of *The Endocrinologist*, our Nurses' article (page 27) once again focuses on nurse-led clinics. This time, the emphasis is on osteoporosis; co-authors Shashana Shalet and Sherwin Criseno have both established and developed nurse-led clinics in this area.

Their article demonstrates the evolving roles of nurses as advanced practitioners, and how application of their skills assists in running such clinics. They highlight how nurses can develop clinics, beginning with the most important aspect: an identified need. The '10 steps' in setting up an osteoporosis clinic are transferable to any type of nurse-led clinic. So if you are looking to set up your own, this advice provides an excellent framework.

Specialist nurses now feel more comfortable with establishing new services. However, two of the most important steps (9 and 10) tend to get forgotten, due to the success of such services and the great demand for them. These steps concern service user feedback and audit, and are therefore essential for the continued improvement and development of the clinic. It is also important to see the clinic as an evolving service, which includes not only its continuous improvement, but professional development of nurses in the specialist area, and steps taken to act on any identified gaps.

Finally, I take this opportunity to thank those who attended, participated in and made Endocrine Nurse Update 2016 in Birmingham in March a success once again. I hope you all have a lovely summer.

LISA SHEPHERD

EVELYN ASHLEY SMITH NURSE AWARDS 2016

Applications for these British Thyroid Foundation awards are now open to endocrine nurses, nurses and healthcare professionals working to help improve care for patients with thyroid disorders. There are two awards: the £500 award can be used to support training needs or conference costs, while the £1,000 award can be used to support a specific one year project or go towards an ongoing piece of work. The application deadline is 1 July 2016 and more information can be found at **http://bit.ly/1WFa9AV**.

NURSE-LED CLINICS FOR OSTEOPOROSIS

WRITTEN BY SHASHANA SHALET & SHERWIN CRISENO

Osteoporosis affects around 6% of men and 21% of women aged 50–84 years in the EU, and is estimated to cost €37 billion per annum.[1] Much of the health and economic cost is due to fragility fractures. Vertebral fractures are frequently missed, and there remains a need for early and accurate diagnosis to reduce mortality and morbidity.[2]

In the last decade, the huge growth in nurse-led clinics (NLCs) has enabled patients to access specialist healthcare in a more timely manner. This area of nursing practice is rapidly becoming an advanced specialism, with many clinics requiring practitioners to undertake physical assessment, care planning, medicines management (e.g. independent or supplementary nurse prescribing), health promotion and health education.[3]

'The NLC is an evolving service. The nurses' knowledge, skills and job descriptions should keep with the pace with changes in osteoporosis practice.'

In setting up an osteoporosis NLC, nurses must consider logistical, management, clinical and financial issues. The '10 essential steps to setting up a service' shown here are adapted from those proposed by Hatchett in 2008.[4]

SHASHANA SHALET
Endocrine Advanced Nurse Practitioner, Salford Royal NHS Foundation Trust

SHERWIN CRISENO
Endocrine Lead Clinical Nurse Specialist, University Hospitals Birmingham NHS Foundation Trust

10 steps to setting up an osteoporosis NLC

1. Build a business case

This explains why the clinic is needed and what it will offer patients and the organisation, and gives a clear overview of the running costs. Several sources of guidance are available, including the Chartered Institute of Personnel Development.[5]

2. Define aims and objectives

The clinic must have well-defined aims. Importantly, defining the objectives will ensure it doesn't duplicate another service in the same Trust.

3. Establish patient criteria

Referral criteria should be clearly defined so only appropriate patients are seen. They should be specific and narrow (e.g. aged ≥65 years, suspected or confirmed fragility fracture/s) and should be available to all potential service users (patients and other healthcare professionals).

4. Create publicity

To ensure success, patients and referrers must know the service exists and what it offers. NLC protocols/guidelines, posters, web information, group discussions and patient information leaflets can be used for publicity.

5. Identify clinic time and location

Issues to take into consideration include the fact that most patients will be elderly, whether the clinic should be held alongside or separate from the consultant clinic, and the availability of administrative support, phlebotomy and bone mineral density X-ray absorptiometry (DXA) scan facilities.

6. Engage multidisciplinary support

An effective clinic must work collaboratively with colleagues in rheumatology, metabolic bone, endocrinology, fracture liaison, nuclear medicine, physiotherapy/occupational therapy, pain management, trauma and orthopaedics, elderly care, phlebotomy and biochemistry, as well as with general practitioners, practice nurses and patient support groups such as the National Osteoporosis Society (NOS), amongst others. Nurses need to know who may refer into their service, who may take their referrals, and who can offer education and advice.

7. Undertake professional development

Nurses should engage in a continuous process of training and supervision to develop their skills in this specific area of advanced practice. Options include case reviews, short courses and conferences (such as the Society for Endocrinology's Endocrine Nurse Update and BES conference, and the NOS conference), as well as observation of existing services and reading around the subject area.

There is no agreed national standard on the professional qualification that nurses require to run an NLC, but the Department of Health has issued guidance on the level of practice expected of nurses working at an advanced level.[6]

8. Plan medicine management

Prescribing vitamin D, calcium and anti-resorptive agents can be an essential part of the clinic. If nurse prescribing is identified as a key aspect of the service, nurses should complete training and ensure they maintain their professional competence in this area.[7,8]

9. Evaluate and audit

Once the service is established, evaluation will ascertain whether it delivers the right care, to the right patient, at the right time, so ensuring that it continues to focus on meeting patients' needs. Others, such as specific organisational audits, may also be required. The process will highlight challenges to the service and provide ideas for future development. Pennery has outlined advice for measuring the effectiveness of a NLC.[9]

10. Close the loop

It is important to understand that the NLC is an evolving service. The nurses' knowledge, guidelines, protocols, job descriptions and audit/evaluation should keep pace with changes in osteoporosis practice. Gaps identified through the audit process should be acted upon within a reasonable time.

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JENS SANDAHL CHRISTIANSEN (1948–2015)

We were deeply saddened when our good friend Jens Sandahl Christiansen passed away in December 2015, following a short illness. Jens Christiansen was Professor of Endocrinology at the University of Aarhus, Denmark, and Consultant in Endocrinology at the Department of Medicine at Aarhus University Hospital.

His contribution as one of the founding fathers in the creation of the European Society of Endocrinology (ESE) was immeasurable, as it moved from a federation-based society to a society with individual membership. He was also integral to the formation of the extremely successful *European Journal of Endocrinology*.

His primary motivation and focus was education, and he always strongly supported ESE's postgraduate activities. His partnership approach regarding ESE's relations with industry helped to place ESE in the strong financial position that it occupies today. He always had an eye on the next generation of endocrinologists and was very keen to support our younger colleagues, and also to ensure that all geographical corners of Europe are empowered to support their own educational activities.

He was involved in so many societies over the years, it is difficult to know where he found the time. In the case of the European Federation of Endocrine Societies (EFES)/ESE he was an active member of several committees and Treasurer (2003–2009), before moving on to support ESE as Chair of the Corporate Liaison Committee. At the time of his death, he was also the serving Editor-in-Chief of *Endocrine Connections*, the official open access journal of ESE and the Society for Endocrinology. He had been Chair of the Local Organising Committee for the extremely successful European Congress of Endocrinology in Copenhagen in 2013.

ESE would not be where it is without Jens's support over the years. We have lost a great scientist, clinician, collaborator and friend. We realise that Jens is irreplaceable and we will miss him greatly, and extend our sincere condolences to his family and close friends.

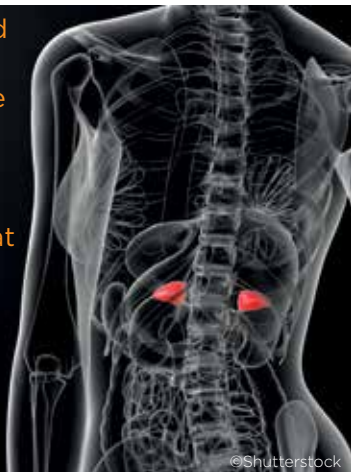
In these sad days, we will raise a glass to honour his spirit – he would have liked that.

AJ VAN DER LELY
ESE President, on behalf of all at ESE

ADRENAL SURGERY – TIME FOR CHANGE

WRITTEN BY JOHN NEWELL-PRICE, JOHN WASS, WIEBKE ARLT & FAUSTO PALAZZO

How comfortable would you be performing a delicate and irreversible task just once a year? How much less comfortable would you be if you performed that task in isolation, and without the benefit of experts to help you make the right choices and to guide any necessary decisions?



It is likely that the answers to these questions are 'not very' and 'much less'.

What would you do if there was someone else available who could do this task and who did it regularly? It seems likely that you would consider, or insist on, getting them to do the task.

AN UNCOMFORTABLE TRUTH

This is not merely a hypothetical proposition. A recent audit of Hospital Episode Statistics (HES) data reveals that, for the 796 operations performed primarily for adrenal disease (excluding nephrectomies) in England during the tax year 2013–2014, the median number of adrenal operations performed per surgeon was … *one*.[1]

Yes, that is not a typo but a stark and uncomfortable fact. Would you refer yourself or your family to such a surgeon, or to a centre where such practice took place? Hopefully not, but that was the fate of nearly 200 individuals who were the only adrenal patient that their surgeon operated upon in that year. Instead, they might have been managed at UK centres that perform 20–30 or more adrenalectomies per annum.

Apart from the 'feelings' and 'uncomfortable emotions' alluded to above, does it matter that these very low volume surgeons are operating in this way? The HES data reveal a significantly longer length of stay and higher 30-day readmission rate for low volume surgeons compared with high volume surgeons, even though the latter are likely to be working in centres attracting more complex adrenal challenges.

The inference is clear: the current situation is causing harm to patients and costing the NHS more. This should come as no surprise to endocrinologists, as we have previously identified similar findings for pituitary and thyroid disease.[2–4] Indeed, the recent clarion call in *New England Journal of Medicine* to 'rid ourselves of low volume surgery'[5] is particularly apposite with regard to these data.

THE VALUE OF TEAMWORK

As endocrinologists, we recognise that the surgeon is only one part of the jigsaw. From diagnosis through to pre-operative preparation, to choosing the right operation for the right person (for example, a transabdominal versus a retroperitoneal laparoscopic approach versus an open procedure), to managing peri-operative and post-operative care, high volume centres have the full range of clinicians, radiologists, clinical chemists, anaesthetists, pathologists, oncologists and nurse specialists working in organised multi-disciplinary teams (MDTs) to offer the best care. It works, as evidenced by the HES data.

Nevertheless, endocrinologists may often be the 'gatekeepers' who control access to adrenal surgery. As such, we have a duty of care to our patients to ensure that they are able to get the best care available, and a duty to the NHS for this to be done in the most time-efficient and cost-effective fashion. This is not the case currently. The number of patients undergoing adrenal operations is still relatively small. This means that to change what we do is achievable, and something where endocrinology truly can 'put its own house in order'.

TAKING ACTION TO MAKE A DIFFERENCE

What then are we to do about this situation? Fuelled by these findings, a cross-disciplinary group has met, with representation from all the surgical specialities, endocrinology, radiology and anaesthetics, to draw up guidance for any patient being considered for adrenal surgery and for adrenal patients in general.

This guidance document has now had 'multi-party' endorsement, including that of the Society for Endocrinology, the Royal College of Physicians, the relevant surgical specialist associations, patient groups and all other parties involved, and is available online.[6]

The recommendations call for all patients being considered for adrenal surgery, all those with functioning adrenal tumours and all those in whom malignancy is suspected to be discussed and managed in centres where there is a formal MDT expert in the management of patients with adrenal disease. The recommendations are not controversial, are common sense, and are backed by evidence.

Moreover, European guidelines on the management of patients with adrenal incidentalomas will be published very soon by the European Society of Endocrinology. These have been drawn up with the involvement of several UK endocrinologists and have been endorsed by several international organisations including the Endocrine Society and the European Network for the Study of Adrenal Tumours.

The clinical endocrinology community needs to rise to this challenge and work together to make a difference to these patients and to the NHS.

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FAUSTO PALAZZO
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THE SOCIETY'S 70 GLORIOUS YEARS: THE 1970S – A TIME OF CHANGE FOR THE JOURNAL

WRITTEN BY BERNARD DONOVAN

As someone much older than the Society for Endocrinology, who has enjoyed membership for more than 50 years, I can add to the reminiscences of past Officers in the Spring issue of *The Endocrinologist*.

A TIME OF WONDER

Endocrinology at the time I joined the Society in 1953 was a wonderland, despite the fact that hormone assays were difficult, expensive and almost always indirect. Assessment of the potency of an extract of an endocrine organ, such as the testis, ovary, adrenal or pituitary gland, usually involved its injection into a series of animals surgically deprived of the organ of interest. Blood levels of hormones could not be measured and immunoassays had still to be devised.

Accordingly, research into endocrinological problems generally involved experimental surgery and there was little sophistication in the equipment employed, other than the need for good microscopes for histological purposes. Electronic equipment, techniques and procedures had still to be developed, and computers were unknown.

Scientific research then differed little from the way in which it was run before the Second World War, although change was on the way. There were more grants for would-be research workers, but few jobs for them after graduation.

I was lucky in that I managed to secure an MRC Scholarship with Geoffrey Harris at the Institute of Psychiatry in London. I prospered, and came to succeed Hans Heller as Editor of *Journal of Endocrinology* in 1974. Having done much refereeing and been a member of the journal's Editorial Board for some years, I was familiar with the refereeing and editorial processes and enjoyed tackling the associated problems that arose.

BECOMING EDITOR

Logically, accepting the Editorship was a silly thing for me to do, for I was busy with research into brain–endocrine relationships and time was already precious. But I had long been interested in scientific writing and publishing, and regarded this appointment as an honour. It was also a challenge.

The first problem posed was to where to base the journal staff. Like many academics, Heller had been able to use departmental space in the Department of Pharmacology at the University of Bristol for this purpose without charge. However, stringencies now meant that the purse strings were being tightened. In my case, there was no spare space available at the Institute of Psychiatry, and none was likely to arise. The future of the staff in Bristol also needed to be considered, for their expertise was highly valued and it made sense to have a permanent base for them.

CHALLENGING COSTS

We accepted that the provision of dedicated accommodation would be expensive and lead to a significant jump in journal production costs, and an analysis of the viability of the journal with the Executive Editorial Secretary, Jean Gardner, proved fascinating.

The pent-up demand for publication of research findings generated by the Second World War had meant that some publishers enjoyed times of plenty, although the librarians, as major purchasers of this material, were beginning to complain of inadequate budgets to pay for the 'outrageous' costs of scientific journals.

We tried to limit price rises by, for example, trying to negotiate reduced prices for the shipment of printed papers by the Post Office, with little success. And with the advent of electric typewriters that had a quality of output approaching that of typeset material, we tried to get our printers to use our office-generated pages without fresh typesetting. But union pressure was such that printers refused to adopt this technique.

Another factor was that the price of a subscription had to be fixed long in advance of publication. That was because time was needed for the subscription agents, who acted for librarians, to advise their clients of upcoming costs in budget planning. Paradoxically, the more successful a journal became in attracting papers, the harder it became to ensure viability, for the printing of more pages generated extra costs that could not easily be recovered. Even so, the demand from researchers to see their papers in print meant that journal publishing, as a commercial activity, thrived.

> ***'We set to work with an enthusiastic staff, and produced the first new issue on our own in January 1975 … the financial benefits were immediately apparent'***

A major factor in our considerations was that our publishing house printed and distributed our journal, along with others, on a commission basis. Remarkably, the publisher found it difficult to separate the cost of publishing our journal from that of others in its stable, and preferred to total all of its costs and charge us an appropriate proportion. Since the staff moved from work on one journal to another in the course of a day, it was hard for them to itemise their charges.

BENEFITS FROM BEING IN CONTROL

When Jean Gardner and I put our findings to the Editorial Board, it was agreed that, despite our inexperience, we should set out to manage all of the production processes 'in house'. While it would be necessary to recruit a printer and distributor to our cause, the overall responsibility for publication would be ours, as would be the rewards (if any).

We set to work with an enthusiastic staff in a house near the centre of Bristol, and produced the first new issue on our own in January 1975, although we did not dare to change the printer until we had settled down.

To our surprise – and delight – while few noticed the change in publisher, the financial benefits were immediately apparent. Rather than being a burden on the coffers, *Journal of Endocrinology* soon became a major source of income, with revenue from the journal increasing substantially between 1974 and 1977 (after transisitional costs had been absorbed). Our success did not pass unnoticed, and our procedures were soon adopted by other societies. That was an immensely satisfying outcome.

BERNARD DONOVAN

Bernard Donovan was Professor of Neuroendocrinology at the Institute of Psychiatry, London, and Editor of Journal of Endocrinology *from 1974 to 1980.*

His book, A Life Scientific: the Memoirs of a Natural Scientist, *has been published by Mereo Books (2015, paperback, £12.99, 407pp, ISBN 978-1861515148) and is widely available.*

Images in ENDOCRINOLOGY

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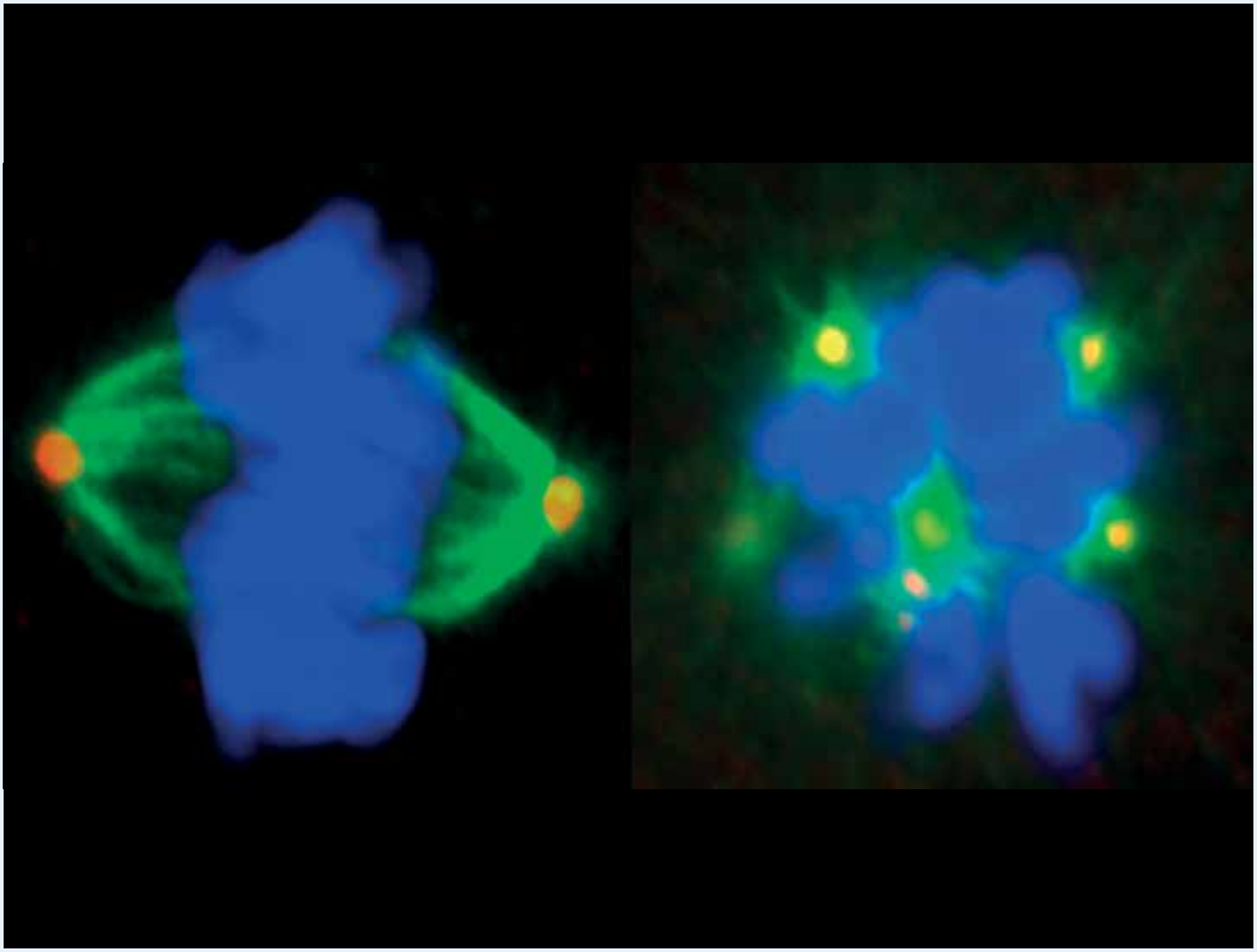
The images depict multipolar mitotic spindles (right) in fibroblasts from a patient with short stature and insulin resistance due to truncation of the centriolar protein POC1A. A bipolar control is also shown (left). (Chen *et al.* 2015 *Journal of Molecular Endocrinology* **55** 147–158.) *Credit: J-H Chen, Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, UK.*



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